(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2007 (12.07.2007)

PCT

(10) International Publication Number
WO 2007/079086 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/4745* (2006.01)
C07D 471/14 (2006.01) *A61K 31/4738* (2006.01)
C07D 231/00 (2006.01) *A61P 31/12* (2006.01)
C07D 231/02 (2006.01) *A61P 31/00* (2006.01)
C07D 471/22 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2006/049307

(22) International Filing Date:
27 December 2006 (27.12.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/743,081 28 December 2005 (28.12.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRAZOLOALKYL SUBSTITUTED IMIDAZO RING COMPOUNDS AND METHODS

(57) Abstract: Imidazo ring compounds, (e.g., imidazo[4,5-*c*]quinoline, 6,7,8,9-tetrahydro imidazo[4,5-*c*]quinoline, imidazo[4,5-*c*]naphthyridine, 6,7,8,9-tetrahydro imidazo[4,5-*c*]naphthyridine and imidazo[4,5-*c*]pyridine compounds) having a pyrazoloalkyl substituent at the 1-position, pharmaceutical compositions containing the compounds, intermediates, and methods of making and methods of use of these compounds as immunomodulators, for modulating cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

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PYRAZOLOALKYL SUBSTITUTED IMIDAZO RING COMPOUNDS AND METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

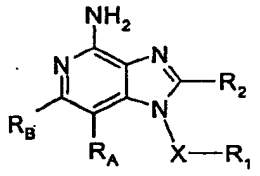
The present invention claims priority to U.S. Provisional Application Serial No. 60/743081, filed December 28, 2005, which is incorporated herein by reference.

BACKGROUND

Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other means.

SUMMARY OF THE INVENTION

It has now been found that certain pyrazoloalkyl substituted ring compounds modulate cytokine biosynthesis. In one aspect, the present invention, therefore, provides a new class of immune response modifying compounds of the following Formula I:



I

wherein X, R_1, R_2, R_A, and R_B are as defined below; and pharmaceutically acceptable salts thereof.

The compounds or salts of Formula I are useful as IRMs due to their ability to modulate cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. The ability to modulate cytokine biosynthesis makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases that are responsive to such changes in the immune response.

In another aspect, the invention further provides pharmaceutical compositions containing an effective amount of a compound of Formula I and methods of inducing cytokine biosynthesis in an animal, treating a viral infection or disease and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula I to the animal.

In a further aspect, methods of synthesizing compounds of Formula I and intermediates useful in the synthesis of these compounds are provided.

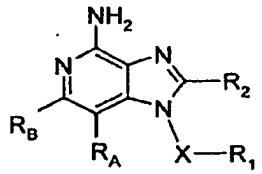
As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

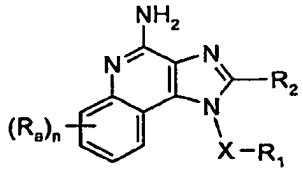
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formula I:

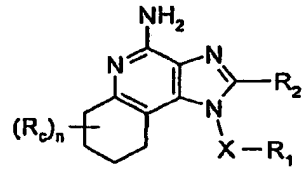


I

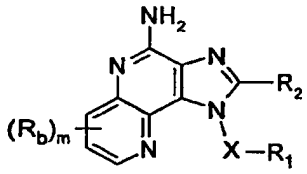
as well as more specific compounds of the following Formulas II through X:



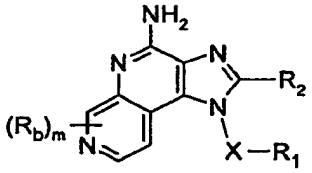
II



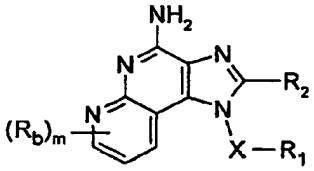
III



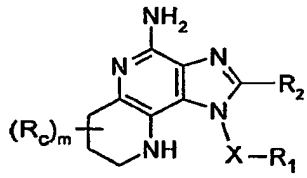
IV



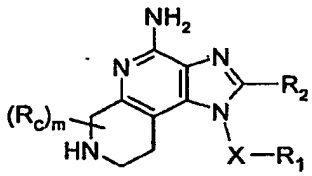
V



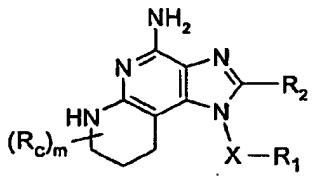
VI



VII



VIII



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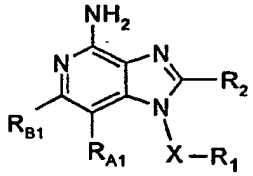
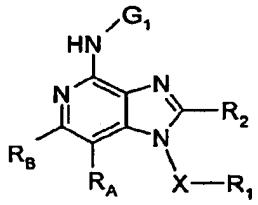


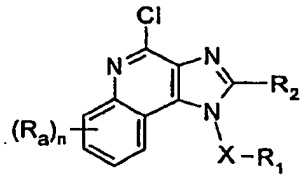
X

prodrugs of the following Formula XI:

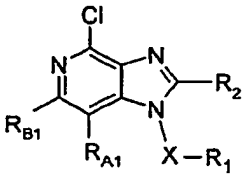


XI

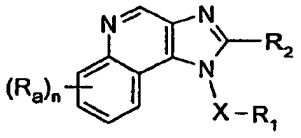
and intermediates of the following Formulas XII through XV:



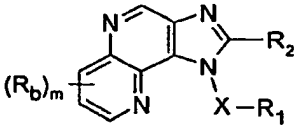
XII



XIII



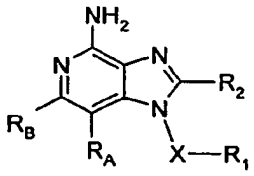
XIV



XV

wherein X, R_1, R_A, R_B, R_{A1}, R_{B1}, R_a, R_b, R_c, R_2, G_1, m, and n are as defined below; and pharmaceutically acceptable salts thereof.

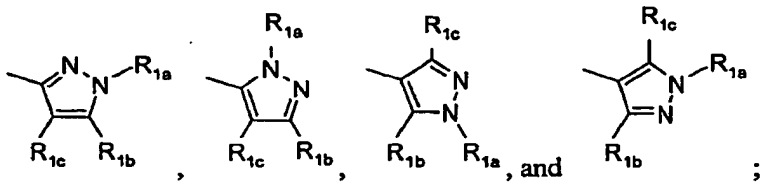
In one embodiment, the present invention provides a compound of the following Formula I:



I

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form either a fused heteroaryl ring that is unsubstituted or substituted by one or more R_b groups, or a 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, and that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-$N(R_5)_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_4)_2$,
$-N(R_4)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

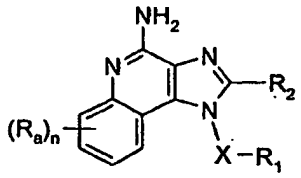
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

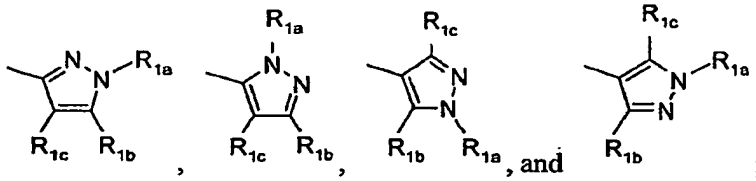
In another embodiment, there is provided a compound of the Formula II:



II

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -$CH(R_3)$- and -$CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

n is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

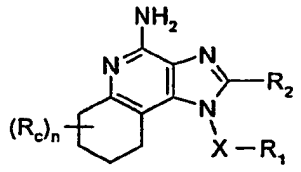
R_8 is selected from the group consisting of hydrogen, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, hydroxy-$C_{1\text{-}10}$ alkylenyl, $C_{1\text{-}10}$ alkoxy-$C_{1\text{-}10}$ alkylenyl, aryl-$C_{1\text{-}10}$ alkylenyl, and heteroaryl-$C_{1\text{-}10}$ alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

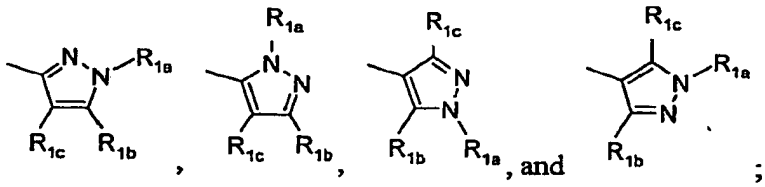
In another embodiment, there is provided a compound of the Formula III:



III

wherein:

R_1 is selected from the group consisting of:



X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-$S(O)_{0-2}$-alkyl,

-$S(O)_{0-2}$-aryl,

-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

n is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups

can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

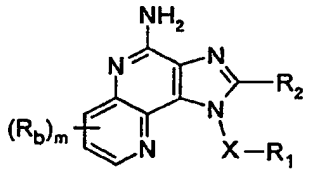
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

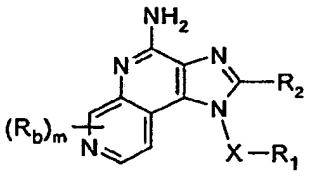
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

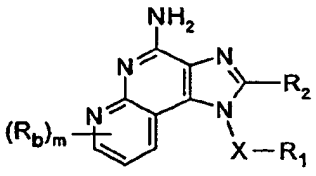
In another embodiment, there is provided a compound selected from the group consisting of the Formulas IV, V, and VI:



IV



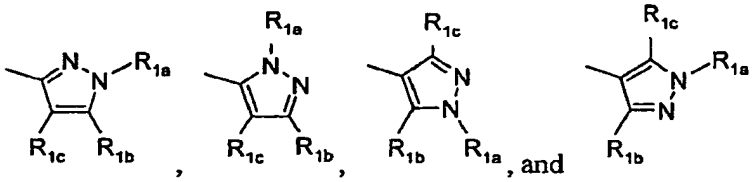
V



VI

wherein:

R_1 is selected from the group consisting of:



; and

X is selected from the group consisting of $-CH(R_3)-$ and $-CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$,

$-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

m is 0, 1, 2, or 3;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

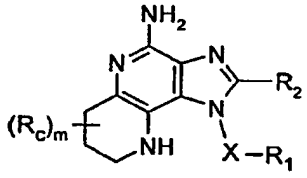
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_5)-; and

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;

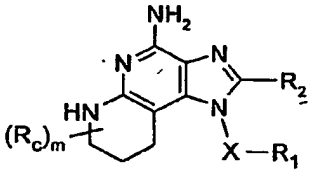
or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound selected from the group consisting of the Formulas VII, VIII, and IX:



VII

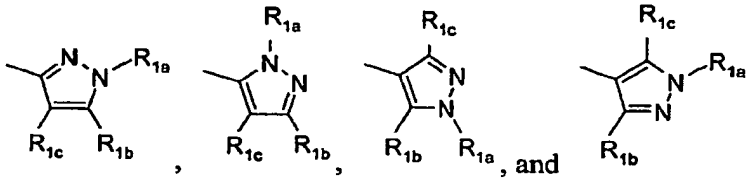
VIII



IX

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

$-C(O)-N(R_4)_2$,

$-N(R_4)-C(O)$-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

m is 0, 1, 2, or 3;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

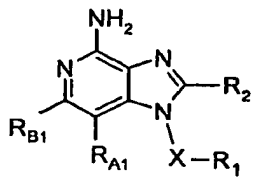
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_5)$-; and

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; d

or a pharmaceutically acceptable salt thereof.

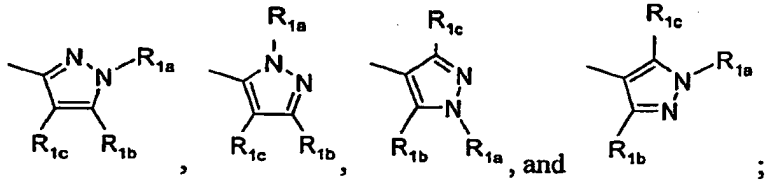
In another embodiment, there is provided a compound of the Formula X:



X

wherein:

R_1 is selected from the group consisting of:



X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-$N(R_5)_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_4)_2$,
$-N(R_4)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

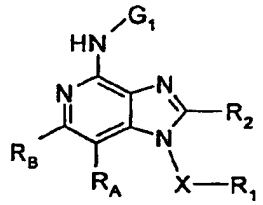
R_8 is selected from the group consisting of hydrogen, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, hydroxy-$C_{1\text{-}10}$ alkylenyl, $C_{1\text{-}10}$ alkoxy-$C_{1\text{-}10}$ alkylenyl, aryl-$C_{1\text{-}10}$ alkylenyl, and heteroaryl-$C_{1\text{-}10}$ alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the following Formula XI, which is a prodrug:



XI

wherein:

G_1 is selected from the group consisting of:

-C(O)-R",

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R",

-C(O)-N(R'")R",

-C(=NY$_1$)-R",

-CH(OH)-C(O)-OY$_1$,

-CH(OC$_{1-4}$ alkyl)Y$_0$,

-CH$_2$Y$_2$, and

-CH(CH$_3$)Y$_2$;

R" and R'" are independently selected from the group consisting of C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, aryl, heteroaryl, aryl-C$_{1-4}$ alkylenyl, heteroaryl-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkoxy, -O-C(O)-CH$_3$, -C(O)-O-CH$_3$, -C(O)-NH$_2$, -O-CH$_2$-C(O)-NH$_2$, -NH$_2$, and -S(O)$_2$-NH$_2$, with the proviso that R'" can also be hydrogen;

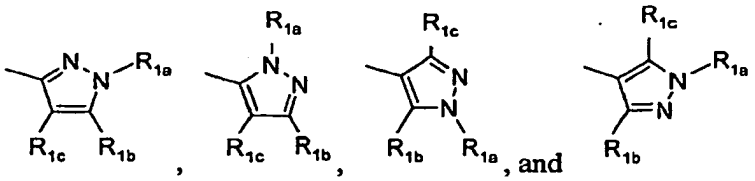
α-aminoacyl is an α-aminoacyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y$_1$ is selected from the group consisting of hydrogen, C$_{1-6}$ alkyl, and benzyl;

Y$_0$ is selected from the group consisting of C$_{1-6}$ alkyl, carboxy-C$_{1-6}$ alkylenyl, amino-C$_{1-4}$ alkylenyl, mono-*N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl, and di-*N,N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl; and

Y$_2$ is selected from the group consisting of mono-*N*-C$_{1-6}$ alkylamino, di-*N,N*-C$_{1-6}$ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C$_{1-4}$ alkylpiperazin-1-yl;

R$_1$ is selected from the group consisting of:



X is selected from the group consisting of -CH(R$_3$)- and -CH(R$_3$)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$, $-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl;

R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form either a fused heteroaryl ring that is unsubstituted or substituted by one or more R_b groups, or a 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, and that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_5)_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_4)_2$,
$-N(R_4)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

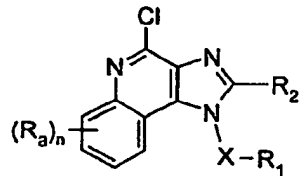
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

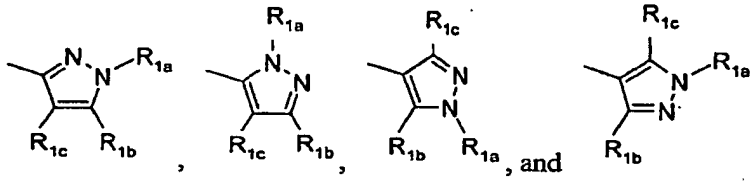
In one embodiment, the present invention provides an intermediate compound of Formula XII:



XII

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -$CH(R_3)$- and -$CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
$-C(O)-O$-alkyl,
$-C(O)-N(R_4)_2$,
$-N(R_4)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

n is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

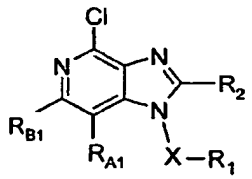
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_5)$-; and

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

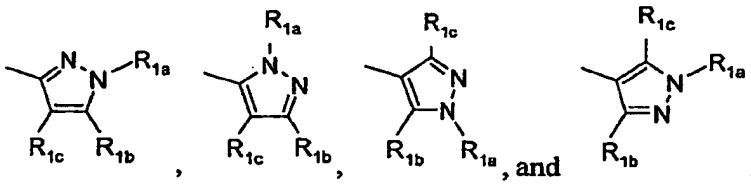
In another embodiment, the present invention provides an intermediate compound of Formula XIII:



XIII

wherein:

R_1 is selected from the group consisting of:



, and ;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-$N(R_5)_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_4)_2$,
$-N(R_4)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

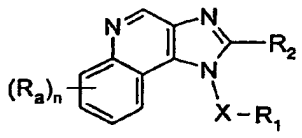
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_5)$-; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

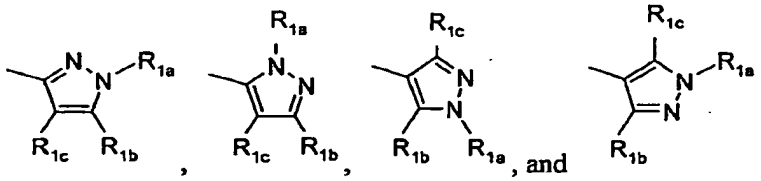
In another embodiment, the present invention provides an intermediate compound of Formula XIV:



XIV

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -$CH(R_3)$- and -$CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$, $-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

n is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

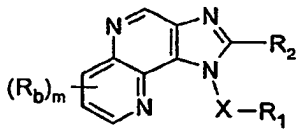
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

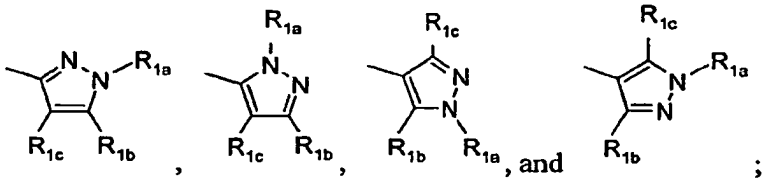
In another embodiment, the present invention provides an intermediate compound of Formula XV:



XV

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of $-CH(R_3)-$ and $-CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$, $-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_4)_2$,
$-N(R_4)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

m is 0, 1, 2, or 3;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g.,

cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are use when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached. In another example, hydroxyalkylenyl, haloalkylenyl, and haloalkyleneoxy have the same meaning as hydroxyalkyl, haloalkyl, and haloalkoxy, respectively.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. In some embodiments, the term "heteroaryl" includes one ring that contains 2-5 carbon atoms, 1-3 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl,

quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. In some embodiments, the term "heterocyclyl" includes one or two rings that contain 2-9 carbon atoms or 2-5 carbon atoms, 1-3 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene", and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

The term "fused aryl ring" includes fused carbocyclic aromatic rings or ring systems. Examples of fused aryl rings include benzo, naphtho, fluoreno, and indeno.

The term "fused heteroaryl ring" includes the fused forms of 5 or 6 membered aromatic rings that contain one heteroatom selected from S and N. Examples of fused heteroaryl rings include pyrido and thieno.

The term "fused 5 to 7 membered saturated ring" includes rings which are fully saturated except for the bond where the ring is fused, for example a cyclohexene ring and a tetrahydropyridine ring (when one nitrogen atom is present).

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-C(O)-N(R_4)_2$ each R_4 group is independently selected. In another example, when two R' groups are present, each R' group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For any of the compounds presented herein, each one of the following variables (e.g., R_1, R_2, R_{1a}, R_{1b}, R_{1c}, R_5, R_7, G_1, Q, X, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and

associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments of Formula I, R_A and R_B taken together form a fused aryl ring that is unsubstituted or substituted by one or more R_a groups. For certain of these embodiments, the fused aryl ring is unsubstituted. For certain embodiments, the fused aryl ring is benzo.

For certain embodiments of Formula I, R_A and R_B taken together form a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups. In certain of these embodiments the ring is unsubstituted. For certain embodiments, the fused 5 to 7 membered saturated ring is a cyclohexene ring.

For certain embodiments of Formula I, R_A and R_B taken together form a fused heteroaryl ring that is unsubstituted or substituted by one or more R_b groups. For certain of these embodiments the fused heteroaryl ring is unsubstituted. In certain embodiments, the ring is pyrido.

For certain embodiments of Formula I, R_A and R_B taken together form a fused 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted or substituted by one or more R_c groups. For certain of these embodiments, the ring is unsubstituted. In certain embodiments, the ring is tetrahydropyrido.

For certain embodiments of Formula X, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_5)_2$.

For certain embodiments of Formula X, R_{A1} and R_{B1} are independently selected from the group consisting of hydrogen and alkyl.

For certain embodiments of Formula X, R_{A1} and R_{B1} are each methyl.

For certain embodiments, including any one of the above embodiments of Formulas II, III, XII, and XIV, n is 0, 1, 2, 3, or 4. For certain of these embodiments, n is 0, 1, or 2. For certain of these embodiments, n is 0 or 1. For certain of these embodiments, n is 0.

For certain embodiments, the compound selected from the group consisting of Formulas IV, V, and VI, or a pharmaceutically acceptable salt thereof is the compound of Formula IV or a pharmaceutically acceptable salt thereof.

For certain embodiments, the compound selected from the group consisting of Formulas VII, VII, and IX, or a pharmaceutically acceptable salt thereof is the compound of Formula VII or a pharmaceutically acceptable salt thereof.

For certain embodiments, including any one of the above embodiments of Formulas IV, V, VI, VII, VIII, IX, and XV, m is 0, 1, 2, or 3. For certain of these embodiments, m is 0, or 1. For certain of these embodiments, m is 0.

For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, R_2 is selected from the group consisting of R_{2a}, R_{2b}, and R_{2c} wherein R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$, $-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl; and R_{2c} is $-NH_2$.

For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$, $-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl.

For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, R_2 is R_{2a}. For certain of these embodiments, R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl. For certain of these embodiments, R_{2a} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4}alkyl-O-C_{1-4}alkylenyl, and hydroxyC_{1-4}alkylenyl. For certain of these embodiments, R_{2a} is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl. For certain of these embodiments, R_{2a} is selected from the group consisting of methyl, ethyl, *n*-propyl, and *n*-butyl.

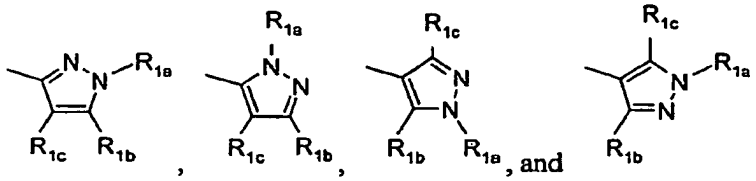
Alternatively, for certain of these embodiments, R_{2a} is selected from the group consisting of methoxymethyl, ethoxymethyl, and 2-methoxyethyl. Alternatively, for certain of these embodiments, R_{2a} is selected from the group consisting of hydroxymethyl and 2-hydroxyethyl.

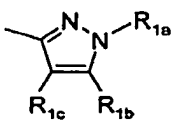
For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, except where R_2 is R_{2a}, R_2 is R_{2b}. For certain of these embodiments, R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$, $-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl. For certain of these embodiments, R_{2b} is $-CH_2-NH-SO_2-CH_3$ or $-CH_2-NH-SO_2-CH_2CH_3$. Alternatively, for certain of these embodiments, including any one of these embodiments of Formulas II, III, X, XII, XIII, and XIV, R_{2b} is $-CH_2-NH-C(O)-C_{1-4}$alkyl. Alternatively, for certain of these embodiments, including any one of these embodiments of Formulas II, III, X, XII, XIII, and XIV, R_{2b} is $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl.

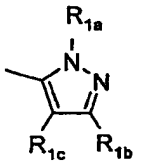
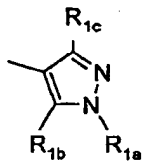
For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, except where R_2 is R_{2a} or R_{2b}, R_2 is R_{2c}.

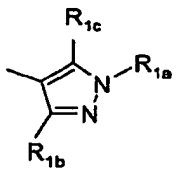
For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, X is selected from the group consisting of $-CH(R_3)-$ and $-CH(R_3)$-alkylene-. For certain of these embodiments, X is C_{1-4} alkylene. For certain of these embodiments, X is $-CH_2-$.

For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, R_1 is selected from the group consisting of:



. For certain of these embodiments, R_1 is  . Alternatively, for certain of these embodiments, R_1 is


. Alternatively, for certain of these embodiments, R_1 is  .


Alternatively, for certain of these embodiments, R_1 is

For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, and alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, dialkylamino, $-S(O)_{0-2}$-alkyl, $-S(O)_{0-2}$-aryl, $-NH-S(O)_2$-alkyl, $-NH-S(O)_2$-aryl, haloalkoxy, halogen, cyano, nitro, aryl, heteroaryl, heterocyclyl, aryloxy, arylalkyleneoxy, -C(O)-O-alkyl, $-C(O)-N(R_4)_2$, $-N(R_4)-C(O)$-alkyl, -O-(CO)-alkyl, and -C(O)-alkyl; with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$. For certain of these embodiments, R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl, wherein alkyl, aryl, and heteroaryl are each unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and haloalkyl. For certain of these embodiments, not more than one of R_{1a}, R_{1b}, and R_{1c} is aryl or heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and haloalkyl. For certain of these embodiments, at least one of R_{1a}, R_{1b}, and R_{1c} is other than hydrogen. For certain of these embodiments, one of R_{1a}, R_{1b}, and R_{1c} is hydrogen. For certain of these embodiments, R_{1c} is hydrogen. For certain of these embodiments, R_{1a} and R_{1b} are independently selected from the group consisting of C_{1-4} alkyl and aryl which is unsubstituted or substituted by one or more substituents independently selected from

fluoro and chloro, and R_{1c} is hydrogen. For certain of these embodiments, R_{1a} and R_{1b} are each independently selected from the group consisting of methyl, 4-fluorophenyl, and 4-chlorophenyl. Alternatively, for certain of these embodiments, R_{1a} is C_{1-4} alkyl, R_{1b} is aryl which is unsubstituted or substituted by one or more substituents independently selected from fluoro and chloro, and R_{1c} is hydrogen. Alternatively, for certain of these embodiments, R_{1a} is aryl which is unsubstituted or substituted by one or more substituents independently selected from fluoro and chloro, R_{1b} is C_{1-4} alkyl, and R_{1c} is hydrogen. For certain of these embodiments aryl is 4-fluorophenyl or 4-chlorophenyl, and C_{1-4} alkyl is methyl.

For certain embodiments, including any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, and XV, except embodiments which exclude the following definition of R_{1b} or R_{1c}, R_{1b} or R_{1c} is $-N(R_5)-Q-R_7$; wherein R_5 is hydrogen or C_{1-4} alkyl, Q is -C(O)-, $-S(O)_2-$, or $-C(O)-N(R_8)$, R_8 is hydrogen or C_{1-4} alkyl, and R_7 is alkyl, aryl, heteroaryl, or heterocyclyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl and heterocyclyl, oxo. For certain of these embodiments, R_{1c} is $-N(R_5)-Q-R_7$, and R_{1a} and R_{1b} are each independently selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl, wherein alkyl, aryl, and heteroaryl are each unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and haloalkyl. Alternatively, for certain of these embodiments, R_{1b} is $-N(R_5)-Q-R_7$, and R_{1a} and R_{1c} are each independently selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl, wherein alkyl, aryl, and heteroaryl are each unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and haloalkyl. For certain of these embodiments where R_{1b} or R_{1c} is $-N(R_5)-Q-R_7$, or where R_{1b} is $-N(R_5)-Q-R_7$, or where R_{1c} is $-N(R_5)-Q-R_7$, R_5 is hydrogen, Q is -C(O)- or $-S(O)_2-$, and R_7 is C_{1-3} alkyl. For certain of these embodiments, $-N(R_5)-Q-R_7$ is methylsulfonylamino, methylcarbonylamino,or cyclopropylcarbonylamino.

For certain embodiments, including any one of the above embodiments of Formula XI or any one of the above embodiments wherein the $-NH_2$ group is replaced by an -NH-G_1 group to form a prodrug as shown in Formula XI, G_1 is selected from the group consisting of -C(O)-R", α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R", -C(O)-N(R'")R", -C(=NY_1)-R", -CH(OH)-C(O)-OY_1, -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_2, and -$CH(CH_3)Y_2$. For certain of these embodiments, R" and R'" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and $-S(O)_2-NH_2$, with the proviso that R'" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y_1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl; and

Y_2 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl.

For certain embodiments, including any one of the above embodiments wherein G_1 is present, G_1 is selected from the group consisting of -C(O)-R", α-aminoacyl, and -C(O)-O-R".

For certain embodiments, including any one of the above embodiments wherein G_1 is present, G_1 is selected from the group consisting of -C(O)-R", α-amino-C_{2-11} acyl, and -C(O)-O-R". α-Amino-C_{2-11} acyl includes α-amino acids containing a total of at least 2 carbon atoms and a total of up to 11 carbon atoms, and may also include one or more heteroatoms selected from the group consisting of O, S, and N.

For certain embodiments, including any one of the above embodiments wherein R_2 is hydroxyalkylenyl, for example, hydroxyC_{1-4} alkylenyl, hydroxymethyl, or 2-

hydroxyethyl, the hydrogen of the hydroxy group is replaced by G_2 to form a prodrug wherein G_2 is selected from the group consisting of $-X_2-C(O)-R''$, α-aminoacyl, α-aminoacyl-α-aminoacyl, $-X_2-C(O)-O-R''$, $-C(O)-N(R''')R''$, and $-S(O)_2-R''$. For certain of these embodiments, X_2 is selected from the group consisting of a bond; $-CH_2-O-$; $-CH(CH_3)-O-$; $-C(CH_3)_2-O-$; and, in the case of $-X_2-C(O)-O-R''$, $-CH_2-NH-$; R'' and R''' are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R''' can also be hydrogen; and α-aminoacyl is an α-aminoacyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from a naturally occuring amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from an amino acid found in proteins, wherein the the amino acid is selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which includes G_2, G_2 is selected from the group consisting of α-amino-C_{2-5} alkanoyl, C_{2-6} alkanoyl, C_{1-6} alkoxycarbonyl, and C_{1-6} alkylcarbamoyl.

For certain embodiments, each R' is independently hydrogen, methyl or ethyl.

For certain embodiments, one R' is hydrogen, and the other R' is methyl.

For certain embodiments, one R' is methyl, and the other R' is methyl.

For certain embodiments, R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl.

For certain embodiments, R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl.

For certain embodiments, R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl.

For certain embodiments, R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl.

For certain embodiments, R_3 is hydrogen.

For certain embodiments, R_3 is methyl.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl.

For certain embodiments, R_4 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_4 is hydrogen.

For certain embodiments, R_5 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_5 is hydrogen.

For certain embodiments, R_5 is C_{1-4} alkyl.

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_6 is =O.

For certain embodiments, R_6 is =S.

For certain embodiments, R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

For certain embodiments, R_7 is alkyl, aryl, heteroaryl, or heterocyclyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy;

heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl and heterocyclyl, oxo.

For certain embodiments, R_7 is C_{1-3} alkyl.

For certain embodiments, R_7 is methyl.

For certain embodiments, R_7 is cyclopropyl.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl.

For certain embodiments, R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_8 is hydrogen.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$.

For certain embodiments, Q is $-C(O)-$, $-S(O)_2-$, or $-C(O)-N(R_8)$.

For certain embodiments, Q is $-C(O)-$ or $-S(O)_2-$.

For certain embodiments, Q is $-C(O)-$.

For certain embodiments, Q is $-S(O)_2-$.

For certain embodiments, W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$.

For certain embodiments, W is a bond.

For certain embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, and XI and a pharmaceutically acceptable carrier.

For certain embodiments, the present invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, and XI or a pharmaceutical composition comprising a therapeutically effective amount of any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, and XI to the animal. For certain of these embodiments, the cytokine is selected from the group consisting of IFN-α, TNF-α, IL-6, IL-10, and IL-12. For certain

of these embodiments, the cytokine is IFN-α or TNF-α. For certain of these embodiments, the cytokine is IFN-α.

For certain embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, and XI or a pharmaceutical composition comprising a therapeutically effective amount of any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, and XI to the animal.

For certain embodiments, the present invention provides a method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, and XI or a pharmaceutical composition comprising a therapeutically effective amount of any one of the above embodiments of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, and XI to the animal.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic

routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

For some embodiments, compounds of the invention can be prepared according to Reaction Scheme I wherein R_a, R_1, R_{2a}, X, and n are as defined above.

In step (1) of Reaction Scheme I, a 2,4-dichloro-3-nitroquinoline of Formula XX is reacted with an amine of Formula R_1-X-NH_2 to provide a compound of Formula XXI. The reaction can be carried out by adding the amine to a solution of the compound of Formula XX in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine. The reaction can be run at ambient temperature or at an elevated temperature such as, for example, 45 °C. Many compounds of Formula XX are known or can be prepared using known synthetic methods, see for example U.S. Patent No. 4,689,338 (Gerster) and U.S. Patent No. 4,988,815 (Andre) and the references cited

therein. Amines of Formula R_1-X-NH_2 can be prepared using known synthetic methods, including those methods described in more detail below.

In step (2) of Reaction Scheme I, a 2-chloro-3-nitroquinoline of Formula XXI is reduced to provide a 2-chloroquinoline-3,4-diamine of Formula XXII. The reduction can be carried out by adding an aqueous solution of sodium dithionite to a solution or suspension of the compound of Formula XXI in a suitable solvent such as ethanol, isopropanol, acetonitrile, or mixtures thereof. The reaction can be carried out at an elevated temperature, for example, at reflux, or at ambient temperature.

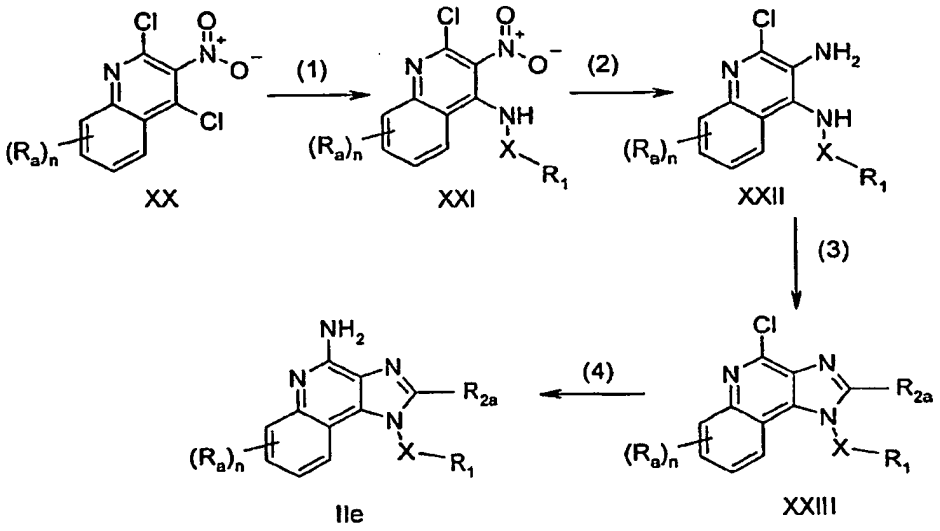
In step (3) of Reaction Scheme I, a 2-chloroquinoline-3,4-diamine of Formula XXII is (i) reacted with an acyl halide of Formula $R_{2a}C(O)Cl$ or $R_{2a}C(O)Br$ and then (ii) cyclized to provide a 4-chloro-1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII. In part (i) the acyl halide is added to a solution of the compound of Formula XXII in a suitable solvent such as acetonitrile or anhydrous dichloromethane in the presence of a base such as triethylamine. The reaction can be run at a sub-ambient temperature, for example, 0° C, or at ambient temperature. In part (ii) the product of part (i) is heated in an alcoholic solvent in the presence of a base. For example, the product of part (i) is refluxed in ethanol in the presence of excess triethylamine or is heated with methanolic ammonia.

Alternatively, step (3) can be carried out by reacting a compound of Formula XXII with a carboxylic acid or an equivalent thereof. Suitable equivalents to carboxylic acid include orthoesters and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired R_{2a} substituent in a compound of Formula XXIII. For example, triethyl orthovalerate will provide a compound where R_{2a} is butyl. The reaction can be run in the absence of solvent or in an inert solvent such as anhydrous toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be utilized.

In step (4) of Reaction Scheme I, a 4-chloro-1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII is reacted with ammonia to provide a 4-amino-1*H*-imidazo[4,5-*c*]quinoline of Formula IIe. The reaction can be carried out by adding a solution of ammonia in a suitable solvent such as methanol to the compound of Formula XXIII and heating the reaction mixture at an elevated temperature such as 150 °C. The reaction can be carried out in a pressure vessel.

Compounds where R_{2a} is hydroxyalkylenyl can be prepared by dealkylation of a methoxy- or ethoxyalkylenyl group, which can be installed by using a methoxy or ethoxy-substituted carboxylic acid equivalent, for example methoxyacetyl chloride, 3-methoxypropionyl chloride, or ethoxyacetyl chloride, in step (3). The dealkylation can be carried out by treating a compound wherein R_{2a} is methoxy- or ethoxyalkylenyl with boron tribromide in a suitable solvent such as dichloromethane at a sub-ambient temperature such as 0 °C. Alternatively an acetoxy substituted carboxylic acid equivalent, for example, acetoxyacetyl chloride, can be used in step (3), and hydrolysis of the ester group to reveal a hydroxy group can be carried out using conventional methods.

Reaction Scheme I



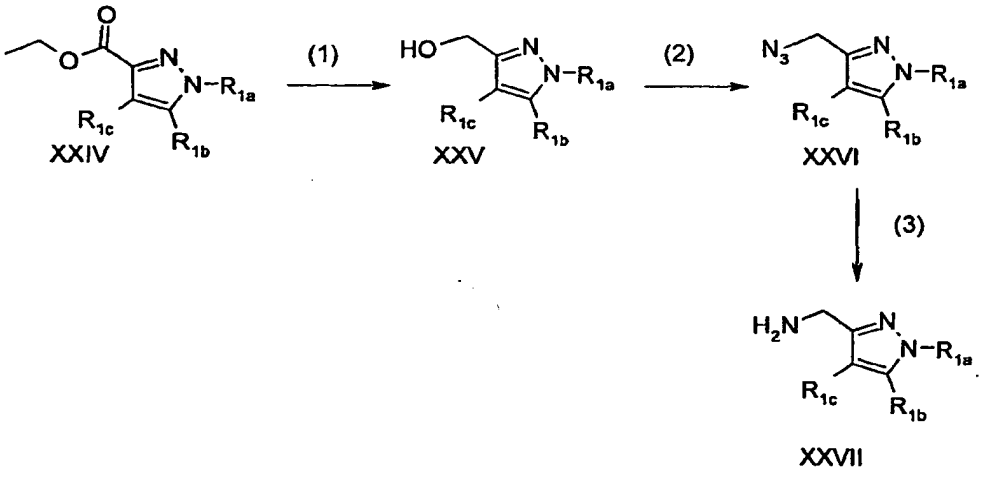
For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme II wherein R_{1a}, R_{1b}, and R_{1c} are as defined above.

In step (1) of Reaction Scheme II, a pyrazole carboxylate of the Formula XXIV is reduced to provide an alcohol of Formula XXV. The reduction can be carried out by treating a solution of the pyrazole carboxylate of Formula XXIV in tetrahydrofuran (THF) with lithium aluminum hydride. The reduction can be carried out at ambient temperature or at a sub-ambient temperature, such as 0 °C. Pyrazole carboxylates of Formula XXIV can be prepared using known synthetic methods, including those methods described in more detail below.

In step (2) of Reaction Scheme II, an alcohol of Formula XXV is converted to an azide of Formula XXVI. The conversion can be carried out in two parts. In part (i) a solution of an alcohol of Formula XXV in a suitable solvent such as dichloromethane is treated with methanesulfonyl chloride in the presence of a base such as triethylamine to provide a sulfonic acid ester. The reaction can be carried out at a sub-ambient temperature, such as -30 °C. Alternatively, in part (i) a solution of an alcohol of Formula XXV in a suitable solvent such as dichloromethane is treated with thionyl chloride to provide a chloride. The reaction can be carried out at ambient temperature. In part (ii) a solution of the sulfonic acid ester or of the chloride in a suitable solvent such as *N,N*-dimethylformamide (DMF) is treated with sodium azide. The reaction can be carried out at ambient temperature.

In step (3) of Reaction Scheme II, an azide of Formula XXVI is reduced to provide an aminomethyl substituted pyrazole of Formula XXVII. The reduction can be carried out using conventional methods such as, for example, catalytic hydrogenation, treatment with triphenylphosphine in the presence of water, and reduction with silicon hydrides catalyzed by organotin reagents.

Reaction Scheme II



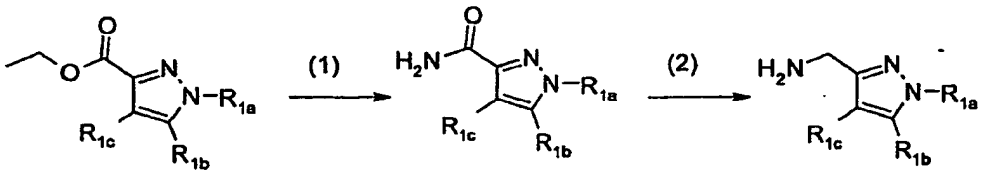
For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme III wherein R_{1a}, R_{1b}, and R_{1c} are as defined above.

In step (1) of Reaction Scheme III, a pyrazole carboxylate of Formula XXIV is converted to a pyrazole carboxamide of Formula XXVIII. The reaction can be carried out by aminating a pyrazole carboxylate of Formula XXIV. The amination can be carried out by adding ammonium hydroxide to a solution of the pyrazole carboxylate of Formula XXIV in a suitable solvent such as methanol and heating at an elevated temperature, such as 100 °C. The reaction can be carried out in a pressure vessel.

Alternatively, step (1) can be carried out in three parts. In part (i) a pyrazole carboxylate of Formula XXIV is hydrolyzed to provide a pyrazole carboxylic acid. The ester hydrolysis can be carried out under basic conditions by combining a solution of the pyrazole carboxylate of Formula XXIV in a suitable solvent such as methanol or ethanol with a solution of lithium hydroxide or sodium hydroxide in water. The reaction can be carried out at ambient temperature. In part (ii) a pyrazole carboxylic acid is converted to a pyrazole acid chloride. The reaction can be carried out by treating a solution of the pyrazole carboxylic acid in a suitable solvent such as dichloromethane with oxalyl chloride. The reaction can be carried out at ambient temperature. In part (iii) the acid chloride is treated with ammonium hydroxide at a sub-ambient temperature, such as 0 °C, to provide a pyrazole carboxamide of Formula XXVIII. Alternatively, the conversion of the carboxylic acid to a pyrazole carboxamide of Formula XXVIII can be carried out under coupling conditions by adding 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride to a solution of the carboxylic acid in a suitable solvent such as DMF at ambient temperature and then adding concentrated ammonium hydroxide.

In step (2) of Reaction Scheme III, a pyrazole carboxamide of Formula XXVIII is reduced to provide an aminomethyl substituted pyrazole of Formula XXVII. The reduction can be carried out using conventional methods, for example, by treating a solution of the pyrazole carboxamide of Formula XXVIII in a suitable solvent such as THF with lithium aluminum hydride or borane.

Reaction Scheme III



XXIV XXVIII XXVII

For some embodiments, pyrazole carboxylate intermediates can be prepared according to Reaction Scheme IV wherein R_{1a} and R_{1b} are as defined above, hal is Br or I, and R_{1d} is defined below.

In step (1) of Reaction Scheme IV, a methyl ketone of Formula XXIX undergoes a Claisen condensation with diethyl oxalate to afford a 1,3-diketone of Formula XXX.

In step (2) of Reaction Scheme IV, a 1,3-diketone of Formula XXX is treated with a hydrazine of Formula $R_{1a}NHNH_2$ to provide the isomeric pyrazoles of Formulas XXXI and XXXII. The reaction can be carried out by slowly adding the hydrazine to a solution of the salt of a compound of Formula XXX in a suitable solvent such as ethanol or acetic acid. The reaction can be carried out at ambient temperature. The isomers can be separated using conventional methods.

In step (3) or (3a) of Reaction Scheme IV, pyrazole carboxylate of Formula XXXI or XXXII is halogenated to provide a pyrazole of Formula XXXIII or XXXIV. Bromination can be carried out by adding bromine to a solution of the pyrazole carboxylate of Formula XXXI or XXXII and potassium acetate in acetic acid. The reaction can be carried out at ambient temperature. Iodination can be carried out by adding iodine monochloride to a mixture of the pyrazole carboxylate of Formula XXXI or XXXII and potassium carbonate in dichloromethane. The reaction can be carried out at ambient temperature.

In step (4) or (4a) of Reaction Scheme IV, a halogenated pyrazole of Formula XXXIII or XXXIV undergoes known palladium-catalyzed coupling reactions such as the Suzuki coupling and the Heck reaction. For example, a compound of Formula XXXIII or XXXIV undergoes Suzuki coupling with a boronic acid of Formula R_{1d}-$B(OH)_2$, an anhydride thereof, or a boronic acid ester of Formula R_{1d}-$B(O\text{-alkyl})_2$; wherein R_{1d} is aryl, heteroaryl, arylalkylenyl, or heteroarylalkylenyl each of which can be unsubstituted or

substituted as defined in R_{1c} above. Numerous boronic acids of Formula R_{1d}-$B(OH)_2$, anhydrides thereof, and boronic acid esters of Formula R_{1d}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods.

The Heck reaction can also be used in Reaction Scheme IV to provide compounds of Formula XXXV or XXXVI, wherein R_{1d} is alkenyl or substituted alkenyl such as, for example, arylalkenyl or heteroaryalkenyl. The Heck reaction is carried out by coupling a compound of Formula XXXIII or XXXIV with a vinyl substituted compound such as, for example, H_2C=C(H)-alkyl, H_2C=C(H)-aryl or H_2C=C(H)-heteroaryl. Several of these vinyl-substituted compounds are commercially available; others can be prepared by known methods. The Suzuki coupling and Heck reaction can be carried out according to any of the methods described in U. S. Patent Application Publication No. 2004/0147543 (Hays et al.). The alkenyl or substituted alkenyl group can be reduced to provide an alkyl or substituted alkyl group. The reduction can be carried out by hydrogenation according to the methods described in U. S. Patent Application Publication No. 2004/0147543 (Hays et al.).

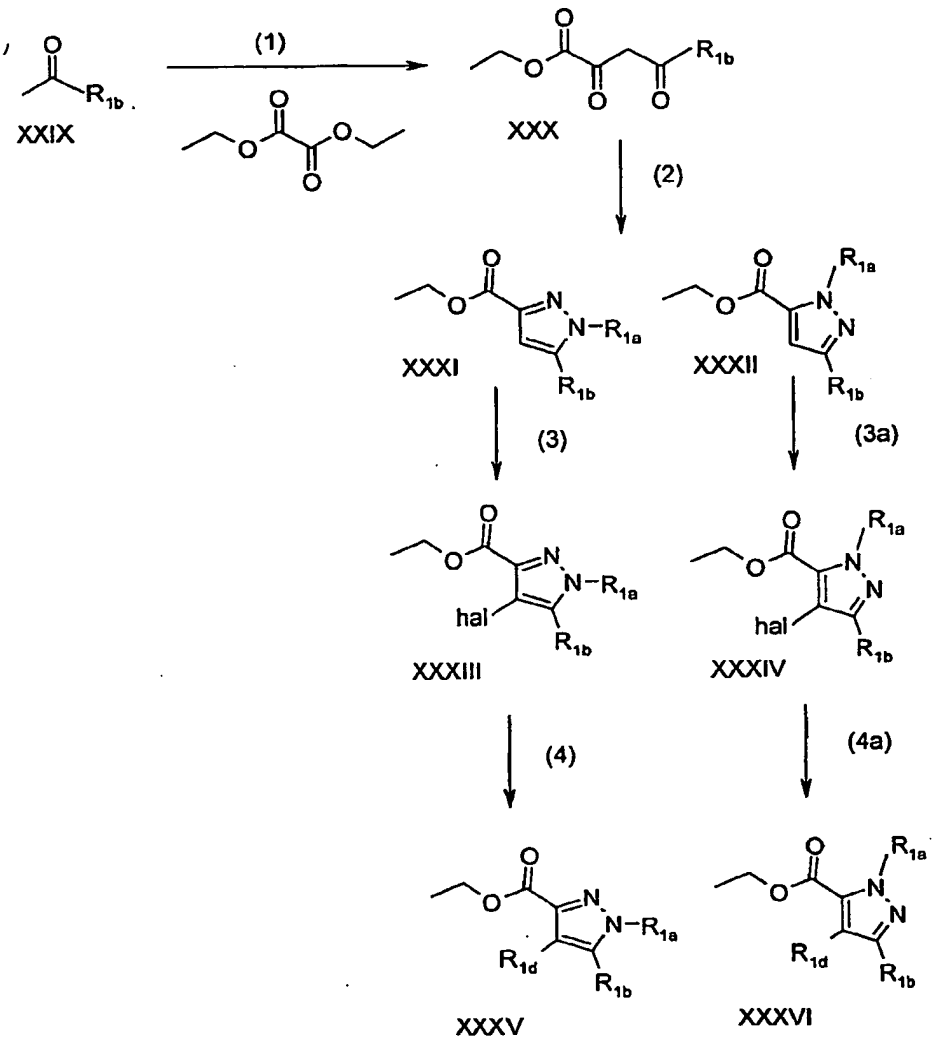
Compounds of Formula XXXV or XXXVI, wherein R_{1d} is an alkynylene or a substituted alkynylene can be prepared by palladium catalyzed coupling reactions such as the Stille coupling or Sonogashira coupling. These reactions are carried out by coupling a compound of Formula XXXIII or XXXIV with an alkyne such as for example, (alkyl)$_3$Sn-C≡C-aryl, (alkyl)$_3$Si-C≡C-aryl, H-C≡C-aryl, (alkyl)$_3$Sn-C≡C-heteroaryl, (alkyl)$_3$Si-C≡C-heteroaryl, or H-C≡C-heteroaryl. The alkynyl or substituted alkynyl group can be reduced to provide an alkyl or substituted alkyl group. The reduction can be carried out by hydrogenation according to the methods described in U. S. Patent Application Publication No. 2004/0147543 (Hays et al.).

A copper-mediated coupling reaction can be used to prepare compounds of Formula XXXV or XXXVI, wherein R_{1d} is -NH-C(O)-alkyl, -NH-SO_2-alkyl, or -NH-SO_2-aryl. The reaction can be carried out by combining a compound of Formula XXXIII or XXXIV and an amide or sulfonamide of Formulas NH_2-C(O)-alkyl, NH_2-SO_2-alkyl, or NH_2-SO_2-aryl in the presence of copper (I) iodide, potassium phosphate, and racemic *trans*-1,2-diaminocyclohexane in a suitable solvent such as 1,4-dioxane. The reaction can be carried out at an elevated temperature such as 110 °C. Many amides and sulfonamides of these formulas are commercially available; others can be

made by conventional methods. These reaction conditions can also be used to couple a compound of Formula XXXIII or XXXIV with a wide variety of nitrogen-containing heterocycles to provide a compound of Formula XXXV or XXXVI wherein R_{1d} is -heterocyclyl wherein the heterocyclyl is attached to the pyrazole ring through a nitrogen atom.

In addition, certain of these compounds of Formula XXXV or XXXVI wherein R_{1d} is -heterocyclyl wherein the heterocyclyl is attached to the pyrazole ring through a nitrogen atom can be prepared using a palladium-mediated coupling, which can be carried out by combining a compound of the Formula XXXIII or XXXIV and the nitrogen-containing heterocyclyl compound in the presence of tris(dibenzylideneacetone)dipalladium, (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, sodium *tert*-butoxide, and a suitable solvent such as toluene. The reaction can be carried out at an elevated temperature such as 80 °C. The synthetic methods described in International Publication No. WO 2005/123080 (Merrill *et al.*) filed June 15, 2005 can also be used. These reaction conditions can also be used to prepare compounds wherein R_{1d} is -NH-R_5.

Reaction Scheme IV



For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme V wherein R_{1a}, R_{1c}, R_5, R_7, and Q are as defined above.

In step (1) of Reaction Scheme V, a nitrile of Formula XXXVII is reacted with diethyl oxalate in the presence of ethanolic sodium ethoxide to afford a cyano ketone of Formula XXXVIII. The reaction can be carried out at ambient temperature and the product isolated as the sodium salt.

In step (2) of Reaction Scheme V, a cyano ketone of Formula XXXVIII is reacted with a hydrazine of formula $R_{1a}NHNH_2$ to afford an aminopyrazole of Formula XXXIX.

The reaction can be carried out in a suitable solvent system such as a mixture of ethanol and acetic acid at elevated temperature, such as the reflux temperature of the solvent system.

In step (3) of Reaction Scheme V, an aminopyrazole of Formula XXXIX is derivatized using conventional methods to provide a compound of Formula XL. For example, a compound of Formula XXXIX can react with an acid chloride of Formula $R_7C(O)Cl$ or acid anhydride of Formula $[R_7C(O)]_2O$ to provide a compound of Formula XL in which Q is -C(O)-. In addition, a compound of Formula XXXIX can react with sulfonyl chloride of Formula $R_7S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_7S(O)_2)_2O$ to provide a compound of Formula XL in which Q is $-S(O)_2-$. Numerous acid chlorides of Formula $R_7C(O)Cl$, sulfonyl chlorides of Formula $R_7S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_7S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out by adding the acid chloride, sulfonyl chloride, or sulfonic anhydride to a solution of the compound of Formula XXXIX in a suitable solvent such as chloroform, dichloromethane, or DMF. Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added.

Sulfamides of Formula XL, where Q is $-S(O)_2-N(R_8)-$, can be prepared by reacting a compound or salt of Formula XXXIX with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula $HN(R_8)R_7$. Alternatively, sulfamides of Formula XL can be prepared by reacting a compound of Formula XXXIX with a sulfamoyl chloride of Formula $R_7(R_8)N-S(O)_2Cl$. Many amines of Formula $HN(R_8)R_7$, and some sulfamoyl chlorides of Formula $R_7(R_8)N-S(O)_2Cl$, are commercially available; others can be prepared using known synthetic methods.

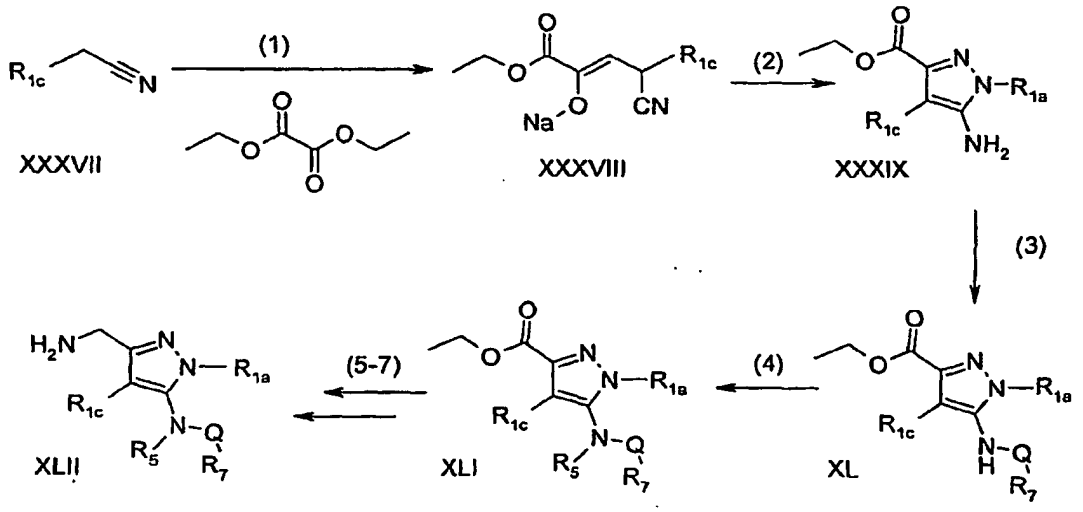
Compounds of Formula XL wherein Q is -C(O)-NH-, $-C(O)-N(R_8)-$, -C(O)-NH-(CO)-, -C(S)-NH-, or $-C(O)-NH-S(O)_2-$ can be prepared by reacting a compound of Formula XXXIX with an isocyanate of Formula $R_7N=C=O$ or carbamoyl chloride of Formula $R_7N-(R_8)-C(R_6)Cl$, an isothiocyanate of Formula $R_7N=C=S$, or a sulfonyl isocyanate of Formula $R_7S(O)_2N=C=O$. Many compounds of these Formulas are commercially available; others can be prepared by known synthetic methods. The reaction can be carried out by adding the isocyanate, isothiocyanate, carbamoyl chloride, or sulfonyl isocyanate to a solution of the compound of Formula XXXIX in a suitable solvent

such as DMF or chloroform. Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added.

In step (4) of Reaction Scheme V, compound of Formula XL is alkylated to provide a compound of Formula XLI. The introduction of an R_5 alkyl group may be achieved by treatment with an alkyl bromide or iodide as described in Wise, L. D. *et al.*, *J. Med. Chem.*, 29, pp. 1628-1637, (1986). When R_5 is hydrogen, step (4) is omitted.

In steps (5) through (7) of Reaction Scheme V, a compound of Formula XLI is converted to an aminomethyl substituted pyrazole of Formula XLII using the methods of steps (1) through (3) respectively of Reaction Scheme II.

Reaction Scheme V



For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme VI wherein R_{1a} and R_{1c} are as defined above and R_{5a}, R_{5b}, and R_{5c} are alkyl.

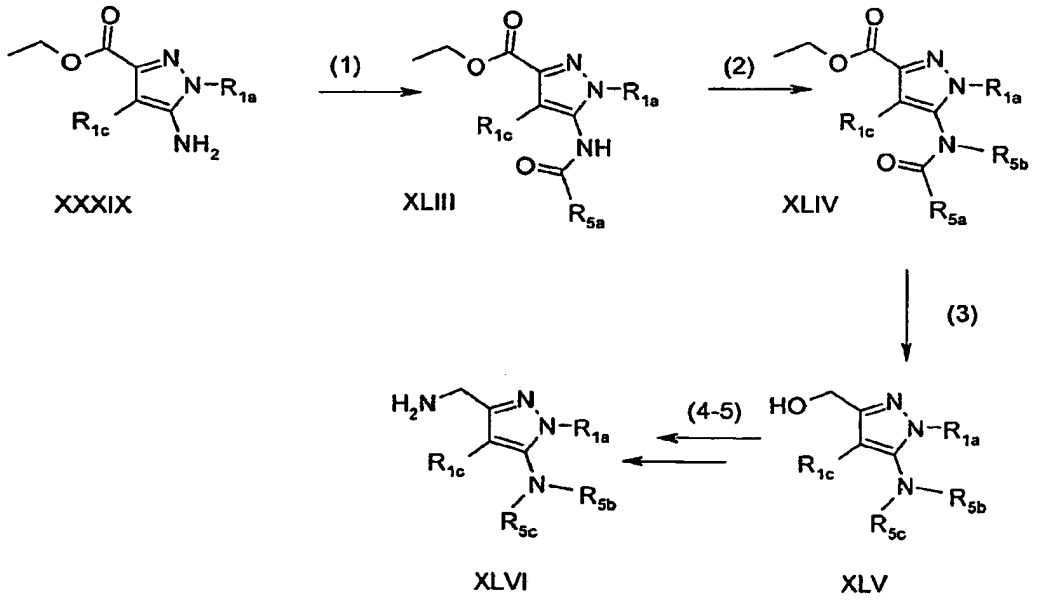
In step (1) of Reaction Scheme VI, an aminopyrazole of Formula XXXIX is converted to an amide of Formula XLIII. The reaction can be carried out as described in step (3) of Reaction Scheme V.

In step (2) of Reaction Scheme VI, an amide of Formula XLIII is alkylated to provide a compound of Formula XLIV. The reaction can be carried out as described in step (4) of Reaction Scheme V.

In step (3) of Reaction Scheme VI, both the amide and the ester groups of a compound of Formula XLIV are reduced to provide a compound of Formula XLV. The reduction can be carried out by treating a solution of a compound of Formula XLIV in a suitable solvent such as THF with lithium aluminum hydride. The reaction can be carried out at an elevated temperature, such as the reflux temperature of the solvent.

In steps (4) and (5) of Reaction Scheme VI, a compound of Formula XLV is converted to an aminomethyl substituted pyrazole of Formula XLVI using the methods of steps (2) and (3) respectively of Reaction Scheme II.

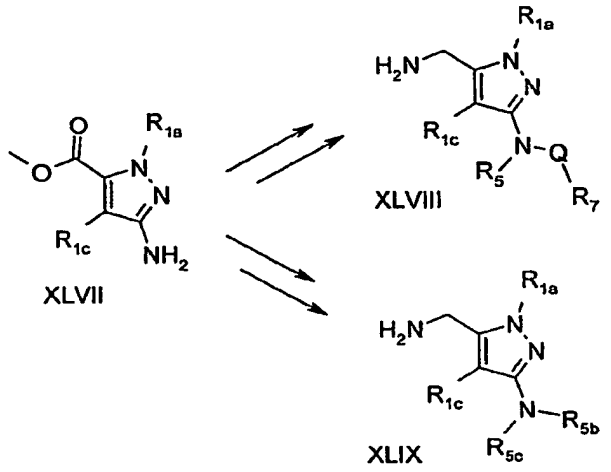
Reaction Scheme VI



For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme VII wherein R_{1a}, R_{1c}, R_5, R_{5b}, R_{5c} R_7, and Q are as defined above.

Aminopyrazole carboxylates of Formula XLVII are known and can be prepared by conventional methods, such as those found in Chenard, B. L. *J. Org. Chem.*, *49*, pp. 1224-1227, (1984) or Lee, H. H. *et al.*, *J. Org. Chem.*, 54, pp. 428-431, (1989). Aminopyrazole carboxylates of Formula XLVII can be converted to compounds of Formula XLVIII using the methods described in Reaction Scheme V. Alternatively, aminopyrazole carboxylates of Formula XLVII can be converted to compounds of Formula XLIX using the methods described in Reaction Scheme VI.

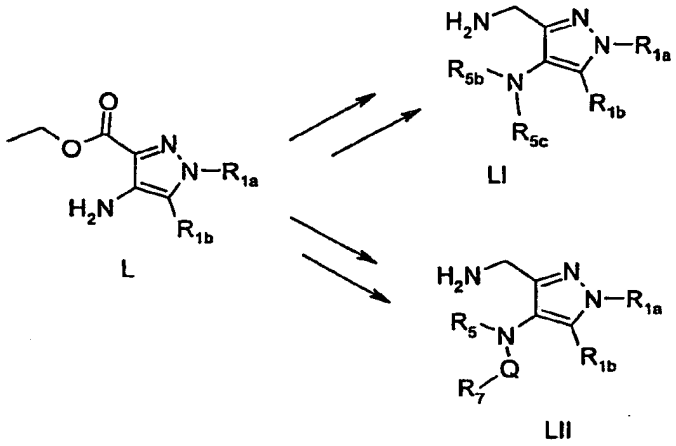
Reaction Scheme VII



For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme VIII wherein R_{1a}, R_{1b}, R_5, R_{5b}, R_{5c} R_7, and Q are as defined above.

Aminopyrazole carboxylates of Formula L are known and can be prepared by conventional methods, such as those found in Yuan, J. *et al.*, *Bioorg. Med. Chem. Lett.*, 12, pp. 2133-2136. Aminopyrazole carboxylates of Formula L can be converted to compounds of Formula LII using the methods described in Reaction Scheme V. Alternatively, aminopyrazole carboxylates of Formula L can be converted to compounds of Formula LI using the methods described in Reaction Scheme VI.

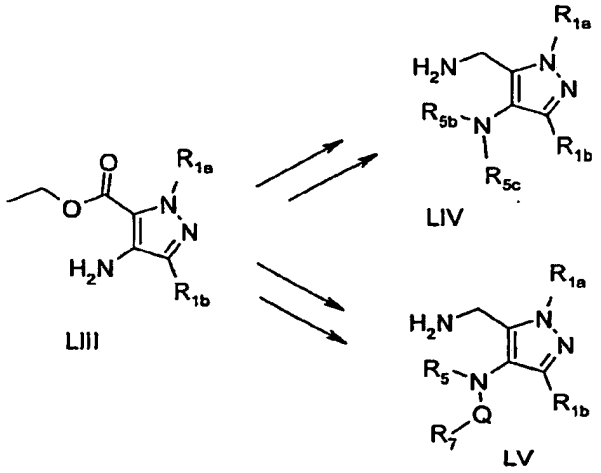
Reaction Scheme VIII



For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme IX wherein R_{1a}, R_{1b}, R_5, R_{5b}, R_{5c} R_7, and Q are as defined above.

Aminopyrazole carboxylates of Formula LIII are known and can be prepared by conventional methods, such as those found in Yuan, J. *et al.*, *Bioorg. Med. Chem. Lett.*, 12, pp. 2133-2136. Aminopyrazole carboxylates of Formula LIII can be converted to compounds of Formula LIV using the methods described in Reaction Scheme VI. Alternatively, aminopyrazole carboxylates of Formula LIII can be converted to compounds of Formula LV using the methods described in Reaction Scheme V.

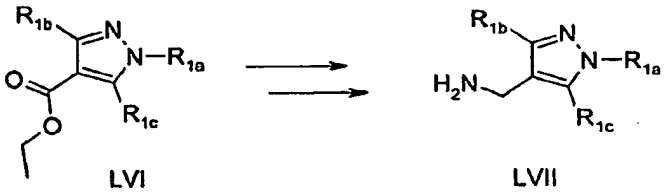
Reaction Scheme IX



For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme X wherein R_{1a}, R_{1b}, and R_{1c} are as defined above.

Pyrazole carboxylates of Formula LVI are known and can be prepared by conventional methods such as those found in Menozzi, G., *et al.*, *J. Heterocycl. Chem.*, 24, pp. 1669-1676, (1987), Huppatz, J. L., *Aust. J. Chem.*, 36, pp. 135-137, (1983), and Rojahn, C. A., *Arch. Pharm.*, 264, pp. 337-347 (1926). They can be converted to aminomethyl substituted pyrazoles of Formula LVII using the methods described in Reaction Schemes II and III.

Reaction Scheme X

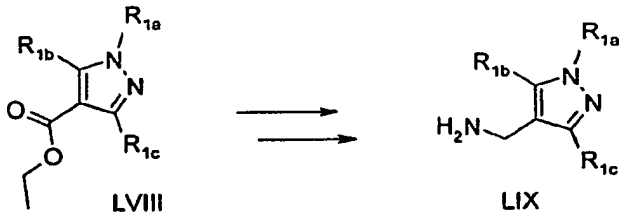


LVI LVII

For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme XI wherein R_{1a}, R_{1b}, and R_{1c} are as defined above.

Pyrazole carboxylates of Formula LVIII are known and can be prepared by conventional methods such as those found in Menozzi, G., *et al.*, *J. Heterocycl. Chem.*, 24, pp. 1669-1676, (1987), and Huppatz, J. L., *Aust. J. Chem.*, 36, pp. 135-137, (1983). They can be converted to aminomethyl substituted pyrazoles of Formula LIX using the methods described in Reaction Schemes II and III.

Reaction Scheme XI

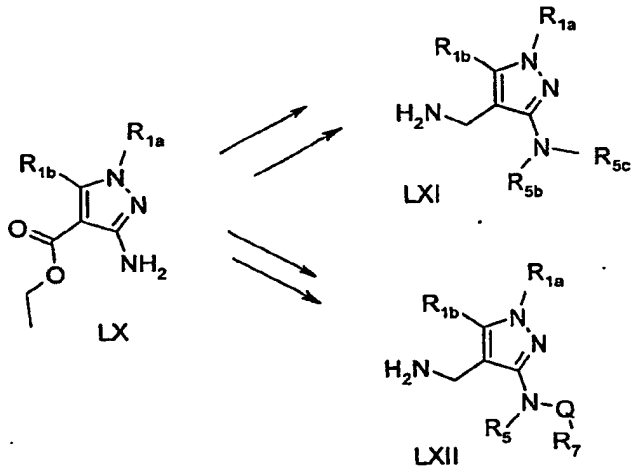


LVIII LIX

For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme XII wherein R_{1a}, R_{1b}, R_5, R_{5b}, R_{5c} R_7, and Q are as defined above.

Aminopyrazole carboxylates of Formula LX are known and can be prepared by conventional methods, such as those found in Senda, S. *et al.*, *Chem. Pharm. Bull.*, 20, pp. 391-398, (1972). Aminopyrazole carboxylates of Formula LX can be converted to compounds of Formula LXII using the methods described in Reaction Scheme V. Alternatively, aminopyrazole carboxylates of Formula LX can be converted to compounds of Formula LXI using the methods described in Reaction Scheme VI.

Reaction Scheme XII

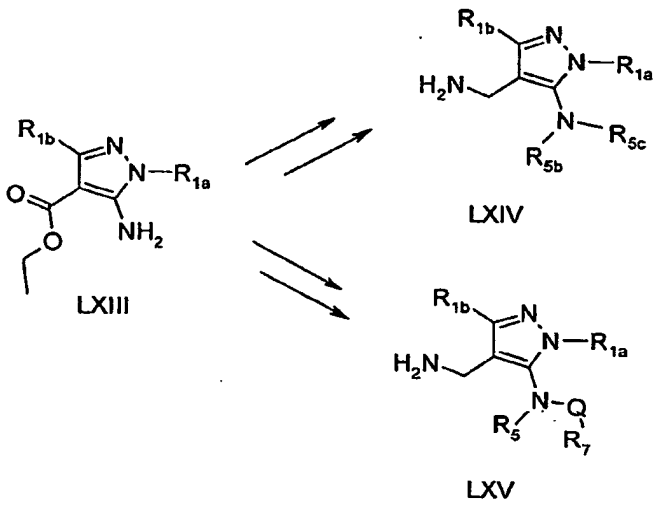


For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme XIII wherein R_{1a}, R_{1b}, R_5, R_{5b}, R_{5c} R_7, and Q are as defined above.

Aminopyrazole carboxylates of Formula LXIII are known and can be prepared by conventional methods, such as those found in Senda, S. *et al.*, *Chem. Pharm. Bull.*, 20, pp. 391-398, (1972) and in Pitt, G. R. W. *et al.*, *Bioorg. Med. Chem. Lett.*, 14, pp. 4585-4589, (2004). Aminopyrazole carboxylates of Formula LXIII can be converted to compounds of Formula LXV using the methods described in Reaction Scheme V. Alternatively,

aminopyrazole carboxylates of Formula LXIII can be converted to compounds of Formula LXIV using the methods described in Reaction Scheme VI.

Reaction Scheme XIII



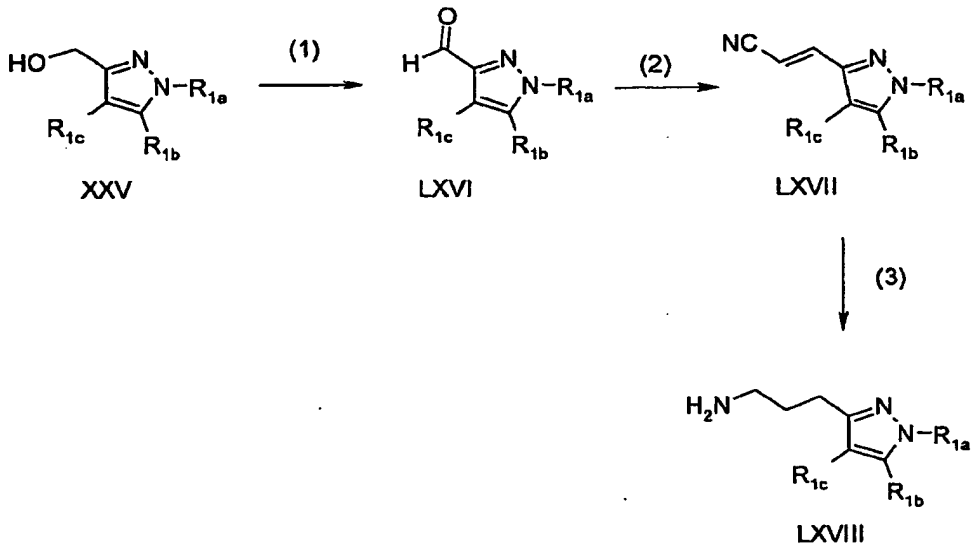
For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme XIV wherein R_{1a}, R_{1b}, and R_{1c} are as defined above.

In step (1) of Reaction Scheme XIV, an alcohol of Formula XXV is oxidized to provide an aldehyde of Formula LXVI. The oxidation can be carried out using conventional methods, such as for example, treatment with manganese dioxide or pyridinium chlorochromate, or Swern conditions.

In step (2) of Reaction Scheme XIV, an aldehyde of Formula LXVI is converted to a nitrile of Formula LXVII. The reaction can be carried out by treating the aldehyde of Formula LXVI with diethyl cyanomethylphosphonate and sodium hydride.

In step (3) of Reaction Scheme XIV, a nitrile of Formula LXVII is reduced to provide an aminopropyl substituted compound of Formula LXVIII. The reduction can be carried out by treating a nitrile of Formula LXVII with lithium aluminum hydride.

Reaction Scheme XIV



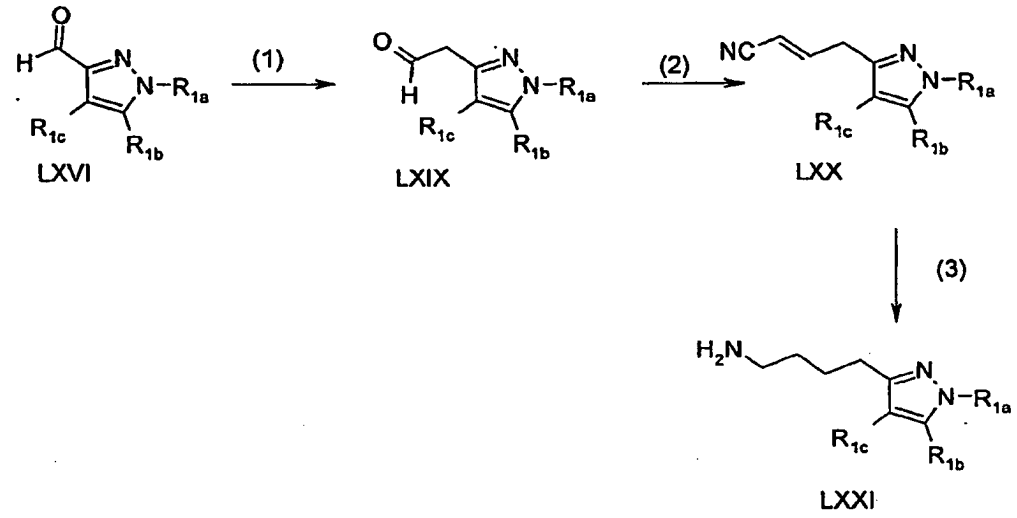
For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme XV wherein R_{1a}, R_{1b}, and R_{1c} are as defined above.

In step (1) of Reaction Scheme XV, an aldehyde of Formula LXVI is homologated to provide an aldehyde of Formula LXIX. The reaction can be carried out in two parts. In part (i) the aldehyde of Formula LXVI is treated with methoxymethylenetriphenylphosphorane and a base such as *n*-butyllithium to provide a vinyl ether. In part (ii) the vinyl ether is hydrolyzed under acidic conditions to provide the aldehyde of Formula LXIX.

In step (2) of Reaction Scheme XV, an aldehyde of Formula LXIX is converted to a nitrile of Formula LXX. The reaction can be carried out by treating the aldehyde of Formula LXIX with diethyl cyanomethylphosphonate and sodium hydride.

In step (3) of Reaction Scheme XV, a nitrile of Formula LXX is reduced to provide an aminobutyl substituted compound of Formula LXXI. The reduction can be carried out by treating a nitrile of Formula LXX with lithium aluminum hydride.

Reaction Scheme XV



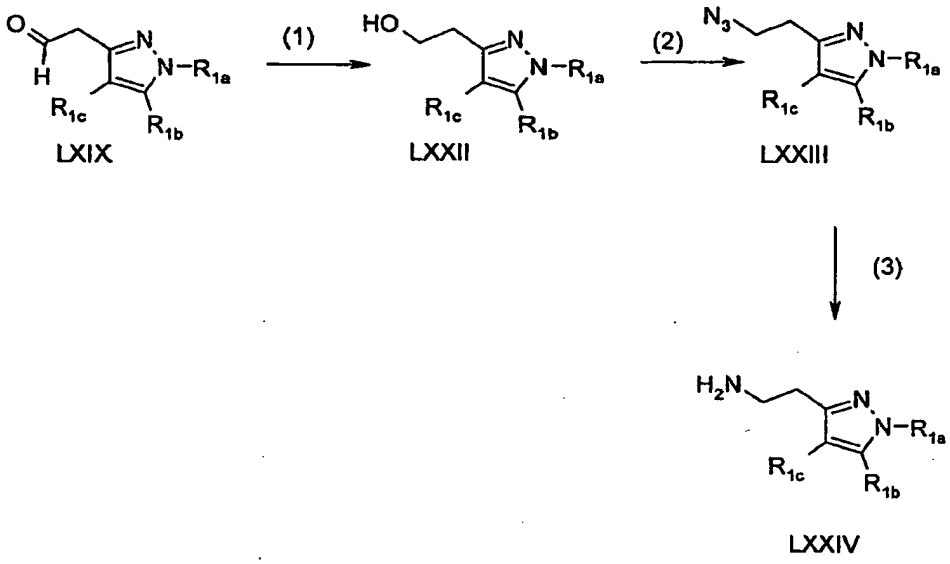
For some embodiments, intermediates of the Formula R_1-X-NH_2 can be prepared according to Reaction Scheme XVI wherein R_{1a}, R_{1b}, and R_{1c} are as defined above.

In step (1) of Reaction Scheme XVI, an aldehyde of Formula LXIX is reduced to provide an alcohol of Formula LXXII. The reduction can be carried out using conventional methods, for example, by treating a solution of the aldehyde of Formula LXIX in ethanol with sodium borohydride.

In step (2) of Reaction Scheme XVI, an alcohol of Formula LXXII is converted to an azide of Formula LXIII using the methods described in step (2) of Reaction Scheme II.

In step (3) of Reaction Scheme XVI, an azide of Formula LXXIII is reduced to provide an aminoethyl substituted pyrazole of Formula LXXIV using the methods described in step (3) of Reaction Scheme II.

Reaction Scheme XVI



For some embodiments, compounds of the invention can be prepared according to Reaction Scheme XVII wherein R_b, R_1, R_{2a}, X, and m are as defined above.

In step (1) of Reaction Scheme XVII, a 4-chloro-3-nitro[1,5]naphthyridine of Formula LXXV is reacted with an amine of Formula R_1-X-NH_2 to provide a 3-nitro[1,5]naphthyridin-4-amine of Formula LXXVI. The reaction can be carried out using the method described in step (1) of Reaction Scheme I. Compounds of Formula LXXV and their preparation are known; see, for example, U.S. Patents Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster).

In step (2) of Reaction Scheme XVII, a 3-nitro[1,5]naphthyridin-4-amine of Formula LXXVI is reduced to provide a [1,5]naphthyridin-3,4-diamine of Formula LXXVII. The reduction can be carried out using the method described in step (2) of Reaction Scheme I.

In step (3) of Reaction Scheme XVII, a [1,5]naphthyridin-3,4-diamine of Formula LXXVII is cyclized to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXVIII. The cyclization can be carried out using the methods described in step (3) of Reaction Scheme I.

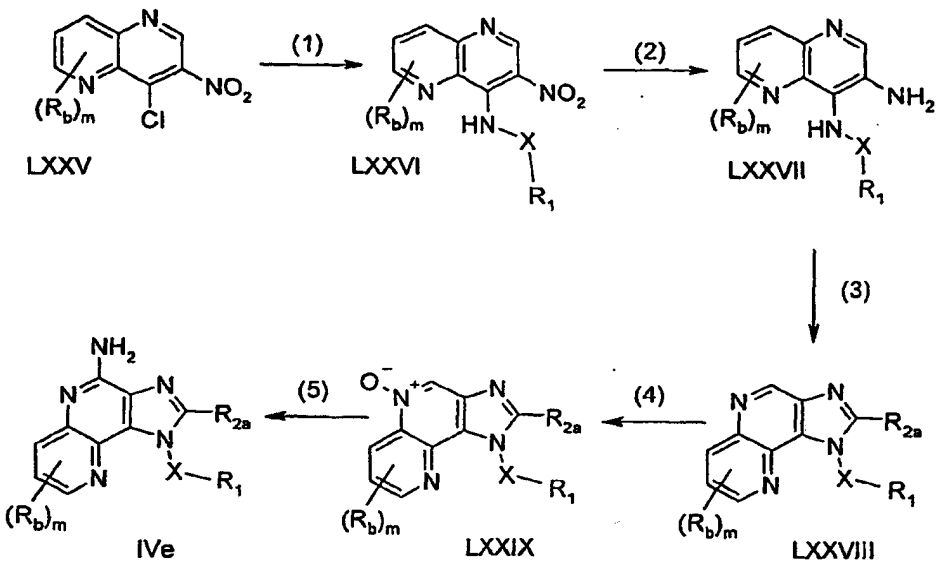
In step (4) of Reaction Scheme XVII, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXVIII is oxidized to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula LXXIX using a conventional oxidizing agent capable of forming *N*-oxides. The reaction can be carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula LXXVIII in a solvent such as dichloromethane or chloroform. The reaction can be carried out at ambient temperature.

In step (5) of Reaction Scheme XVII, a 5*N*-oxide of Formula LXXIX is aminated to provide a 1*H*-imidazo[4,5-*c*][1,5]napthyridin-4-amine of Formula IVe. Step (5) can be carried out by the activation of an *N*-oxide of Formula LXXIX by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction can be carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula LXXIX in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride or benzenesulfonyl chloride. The reaction can be carried out at ambient temperature.

Steps (4) and (5) of Reaction Scheme XVII may be carried out as a one-pot procedure by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula LXXVIII in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride or benzenesulfonyl chloride without isolating the *N*-oxide compound of Formula LXXIX.

The amination reaction in step (5) of Reaction Scheme XVII can alternatively be carried out by treating a 5*N*-oxide of Formula LXXIX with trichloroacetyl isocyanate followed by hydrolysis of the resulting intermediate to provide a compound of Formula IVe. The reaction is carried out in two steps by (i) adding trichloroacetyl isocyanate to a solution of a 5*N*-oxide of Formula LXXIX in a solvent such as dichloromethane and stirring at ambient temperature to provide an isolable amide intermediate. In step (ii), a solution of the intermediate in methanol is treated with a base such as sodium methoxide or ammonium hydroxide at ambient temperature.

Reaction Scheme XVII



For some embodiments, compounds of the invention can be prepared according to Reaction Scheme XVIII wherein R_1, R_{2a}, R_{A1}, R_{B1}, and X are as defined above and PMB is *para*-methoxybenzyl.

In step (1) of Reaction Scheme XVIII, a 2,4-dichloro-3-nitropyridine of Formula LXXX is reacted with an amine of Formula R_1-X-NH_2 to provide a 2-chloro-3-nitropyridine of Formula LXXXI. The reaction can be carried out using the method described in step (1) of Reaction Scheme I. Many 2,4-dichloro-3-nitropyridines of the Formula LXXX are known and can be readily prepared using known synthetic methods. (See, for example, Dellaria et al., U.S. Pat. No. 6,525,064 and the references cited therein.)

In step (2) of Reaction Scheme XVIII, a 2-chloro-3-nitropyridine of Formula LXXXI is reacted with *bis*-(4-methoxybenzyl)amine to provide an *N*-{2-[*bis*-(4-methoxybenzyl)amino]-3-nitropyridine of Formula LXXXII. The reaction can be carried out by adding the *bis*-(4-methoxybenzyl)amine to a solution of a compound of Formula LXXXI in a suitable solvent such as toluene in the presence of a base such as triethylamine. The reaction can be carried out at an elevated temperature (about 90 °C).

In step (3) of Reaction Scheme XVIII, an N^2-{2-[*bis*-(4-methoxybenzyl)amino]-3-nitropyridine of Formula LXXXII is reduced to provide an N^2-[*bis*-(4-

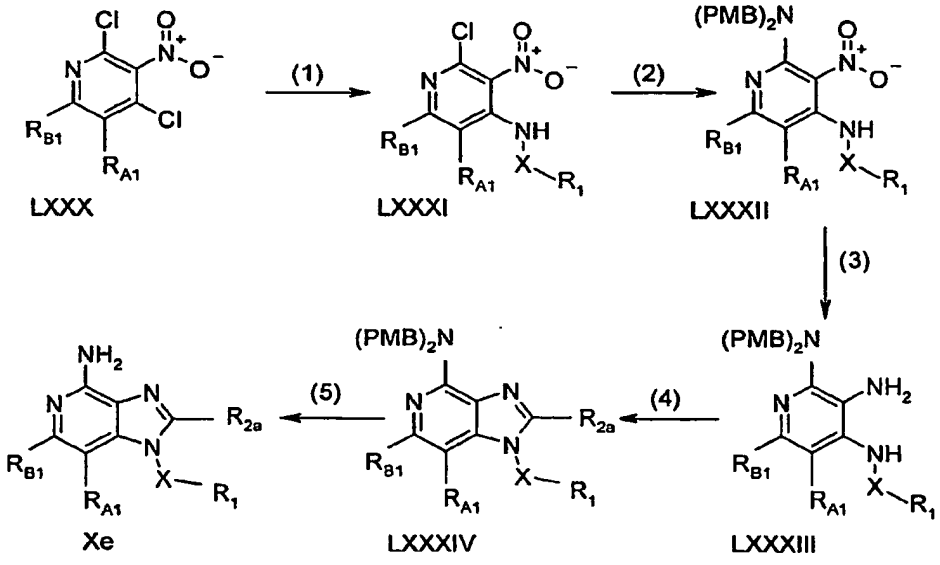
methoxybenzyl)]pyridine-2,3,4-triamine of Formula LXXXIII. The reduction can be carried out using the method described in step (2) of Reaction Scheme I.

In step (4) of Reaction Scheme XVIII, an N^2-[*bis*-(4-methoxybenzyl)]pyridine-2,3,4-triamine of Formula LXXXIII is cyclized to provide an *N*-[*bis*-(4-methoxybenzyl)]-1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula LXXXIV. The cyclization can be carried out using the methods described in step (3) of Reaction Scheme I.

In step (5) of Reaction Scheme XVIII, the 4-methoxybenzyl groups on an *N*-[*bis*-(4-methoxybenzyl)]-1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula LXXXIV are removed by acid hydrolysis to provide a 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula Xe. The reaction can be carried out by treating a compound of Formula LXXXIV with trifluoroacetic acid. The reaction can be carried out at ambient temperature.

Alternatively, the *bis*-(4-methoxybenzyl)amino group may be installed at a later point in the synthesis, e.g. after cyclization.

Reaction Scheme XVIII



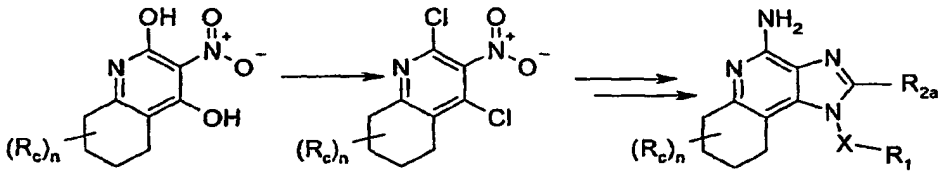
For some embodiments, compounds of the invention can be prepared according to Reaction Scheme XIX wherein R_c, R_1, R_{2a}, X, and n are as defined above.

In step (1) of Reaction Scheme XIX, a 2,4-dihydroxy-3-nitrotetrahydroquinoline of Formula LXXXV is chlorinated to provide a 2,4-dichloro-3-nitrotetrahydroquinoline of

Formula LXXXVI. The reaction can be carried out by combining a compound of Formula LXXXV with a conventional chlorinating agent (e.g., phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride, or phosphorus pentachloride), optionally in a solvent such as DMF or dichloromethane. The reaction can be run at an elevated temperature. Some 2,4-dihydroxy-3-nitrotetrahydroquinolines of Formula LXXXV are known; others can be prepared using known synthetic routes, see for example, U.S. Patent No. 5,352,784 (Nikolaides).

A 2,4-dichloro-3-nitrotetrahydroquinoline of Formula LXXXVI is then converted to a tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula VIIe using the methods described in steps (1) through (4) of Reaction Scheme I.

Reaction Scheme XIX



LXXXV LXXXVI VIIe

For some embodiments, compounds of the invention can be prepared according to Reaction Scheme XX wherein R_a, R_1, R_{2b}, X, and n are as defined above.

In step (1) of Reaction Scheme XX, a 4-chloro-3-nitroquinoline of Formula LXXXVII is reacted with an amine of Formula R_1-X-NH_2 to provide a 3-nitroquinolin-4-amine of Formula LXXXVIII. The reaction can be carried out using the method described in step (1) of Reaction Scheme I.

In step (2) of Reaction Scheme XX, a 3-nitroquinolin-4-amine of Formula LXXXVIII is reduced to provide a quinolin-3,4-diamine of Formula LXXXIX. The reduction can be carried out using the method described in step (2) of Reaction Scheme I.

In step (3) of Reaction Scheme XX, a quinolin-3,4-diamine of Formula LXXXIX is reacted with chloroacetyl chloride to provide a 2-chloromethyl-1*H*-imidazo[4,5-*c*]quinoline of Formula XC. The reaction can be carried out using the method described in step (3) of Reaction Scheme I.

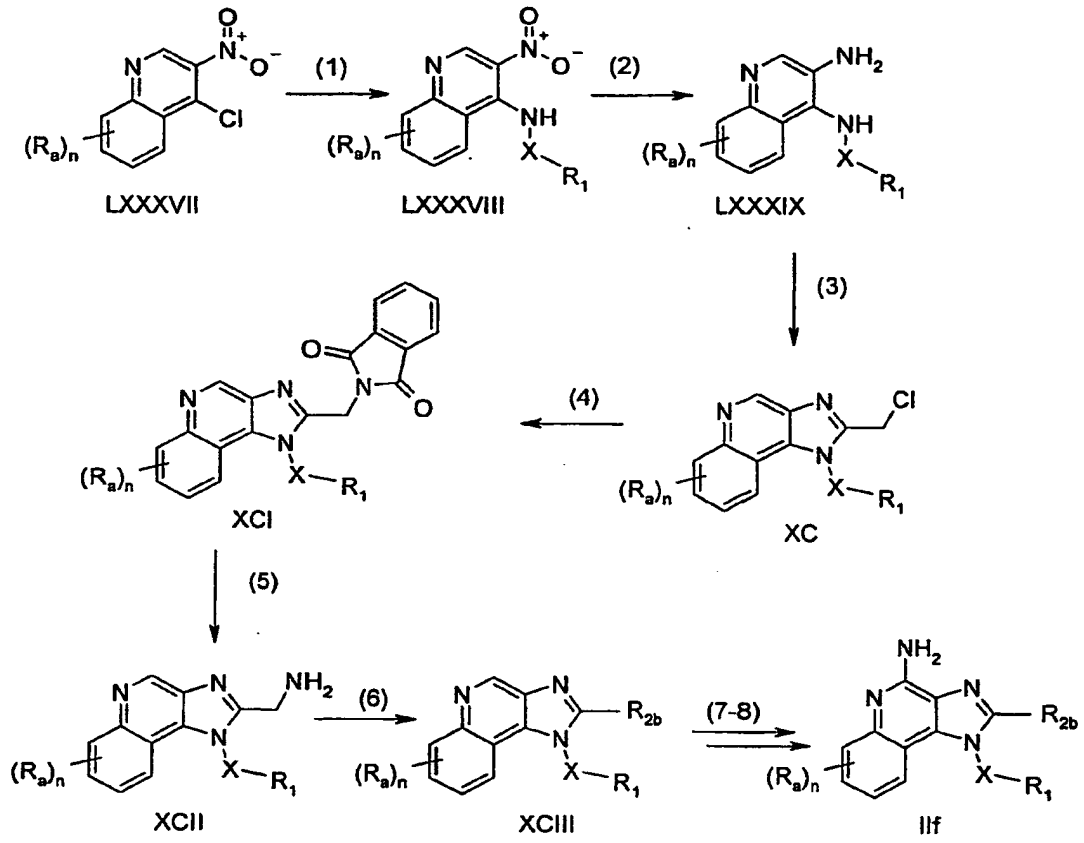
In step (4) of Reaction Scheme XX, a 2-chloromethyl-1*H*-imidazo[4,5-*c*]quinoline of Formula XC is treated with potassium phthalimide to provide a phthalimide-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XCI. The reaction can be carried out by combining potassium phthalimide and a compound of Formula XC in a suitable solvent such as DMF. The reaction can be carried out at ambient temperature.

In step (5) of Reaction Scheme XX, a phthalimide-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XCI is deprotected to provide a 2-aminomethyl-1*H*-imidazo[4,5-*c*]quinoline of Formula XCII. The phthalimide protecting group can be removed by adding hydrazine to a suspension of the compound of Formula XCI in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature.

In step (6) of Reaction Scheme XX, the amino group of a 2-aminomethyl-1*H*-imidazo[4,5-*c*]quinoline of Formula XCII is derivatized to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XCIII. The derivatization can be carried out using the methods described in step (3) of Reaction Scheme V.

In steps (7) and (8) of Reaction Scheme XX, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XCIII is oxidized and then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula IIf using the methods described in steps (4) and (5) of Reaction Scheme XVII.

Reaction Scheme XX



The aminoalkyl substituted pyrazoles described above can be used to prepare 1*H*-imidazo[1,7]naphthyridin-4-amines and 1*H*-imidazo[1,8]naphthyridin-4-amines of the invention using the general methods described in U.S. Patent No. 6,194,425 (Gerster).

Compounds wherein R_2 is -NH_2 can be prepared using the methods disclosed in International Publication No.WO 2006/029115 (Kshirsagar *et al.*).

Compounds of the invention can also be prepared using variations in the synthetic routes shown in Reaction Schemes I through XX that would be apparent to one of skill in the art. For example, the pyrazole carboxylates of Formulas LVI and LVIII can be reduced to the corresponding alcohols using the method of step (1) of Reaction Scheme II and the alcohols can be converted to the corresponding chain extended aminoalkyl substituted pyrazoles using the methods of Reaction Schemes XIV, XV, and XVI. Also,

the methods used in Reaction Scheme XX to install a R_{2b} group on a 1*H*-imidazo[4,5-*c*]quinoline can also be used to prepare 1*H*-imidazo[4,5-*c*]pyridines, 1*H*-imidazo[4,5-*c*]napthyridines, and tetrahydro-1*H*-imidazo[4,5-*c*]quinolines. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Prodrugs can be prepared in a variety of ways. For example, a compound wherein R_{2a} is hydroxyalkylenyl can be converted into a prodrug by replacing the hydrogen of the hydroxy group with G_2 wherein G_2 is selected from the group consisting of -X_2-C(O)-R", α-aminoacyl, α-aminoacyl-α-aminoacyl, -X_2-C(O)-O-R", -C(O)-N(R'")R", and -$S(O)_2$-R". For certain of these embodiments, X_2 is selected from the group consisting of a bond; -CH_2-O-; -$CH(CH_3)$-O-; -$C(CH_3)_2$-O-; and, in the case of -X_2-C(O)-O-R", -CH_2-NH-; R" and R'" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and -$S(O)_2$-NH_2, with the proviso that R'" can also be hydrogen; and α-aminoacyl is an α-aminoacyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids. In addition, a compound wherein R_b or R_c is hydroxy may also be converted to an ester, an ether, a carbonate, or carbamate. For compounds containing an alcohol functional group, particularly useful prodrugs are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from naturally occurring L-amino acids.

Prodrugs can also be made from a compound containing an amino group by conversion of the amino group to a functional group such as an amide, carbamate, urea, amidine, or another hydrolyzable group using conventional methods. A prodrug of this type can be made by the replacement of a hydrogen atom in an amino group, particularly the amino group at the 4-position, with a group such as -C(O)-R", α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R", -C(O)-N(R'")-R", –C(=NY_1)-R", -CH(OH)-C(O)-OY_1, -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_2, or -$CH(CH_3)Y_2$; wherein R" and R'" are each independently C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, or benzyl, each of which may

be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and -$S(O)_2$-NH_2; each α-aminoacyl group is independently selected from the naturally occurring racemic, D-, and L-amino acids; Y_1 is hydrogen, C_{1-6} alkyl, or benzyl; Y_0 is C_{1-6} alkyl, carboxyC_{1-6} alkyl, aminoC_{1-4} alkyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkyl, or di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkyl; and Y_2 is mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, or 4-C_{1-4} alkylpiperazin-1-yl.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, computed according to the Dubois method, in which the body surface area of a subject (m^2) is computed using the subject's body weight: $m^2 = (wt\ kg^{0.425} \times height\ cm^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some

of these embodiments, the method includes administering sufficient compound to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/ m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to

the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts described herein can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts described herein can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria,

hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments the induction or inhibition of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an

effective amount of a compound or salt of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

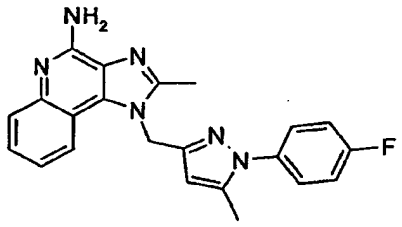
EXAMPLES

In the examples below normal high performance flash chromatography (prep HPLC) was carried out using a COMBIFLASH system (an automated high-performance flash purification product available from Teledyne Isco, Inc., Lincoln, Nebraska, USA), a

HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA) or an INTELLIFLASH Flash Chromatography System (an automated flash purification system available from AnaLogix, Inc, Burlington, Wisconsin, USA). The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Example 1

1-{[1-(4-Fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

4-Fluorophenylhydrazine hydrochloride (25.0 g, 0.154 mol) was added in one portion to a solution of potassium acetate (16.6 g, 0.169 mol) and ethyl acetopyruvate (24.3 g, 0.154 mol) in ethanol (0.154 L). After stirring overnight, methyl *tert*-butyl ether (0.150 L) was added, the resulting solid was removed by filtration, and the filtrate was concentrated to 40 g of dark oil. This was dissolved in chloroform (100 g), divided into two equal portions, and each portion was purified by prep HPLC (silica cartridge, eluting with 25% to 40% ethyl acetate in hexane) to separate the two pyrazole isomers. The fractions from both purifications that contained the lower running isomer were combined and concentrated to yield 15.81 g of ethyl 1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate as an orange oil. The fractions from both purifications that contained the higher running isomer were combined and concentrated to yield 9.58 g of ethyl 1-(4-fluorophenyl)-3-methyl-1*H*-pyrazole-5-carboxylate as an orange solid.

Part B

Ethyl 1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (10.58 g, 42.6 mmol) was dissolved in THF (25 mL) and added via syringe to an ice-cold solution of $LiAlH_4$ (42.6 mL of a 1 M solution in THF). The ice bath was removed; the reaction was stirred for 30 minutes, cooled again in an ice bath, and then quenched by the addition of water (1.6 mL), 4N sodium hydroxide (1.6 mL) and water (4.8 mL). The resulting solid was removed by filtration through CELITE, and the filtrate was concentrated to afford 8.07 g of [1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methanol as an orange solid.

Part C

A solution of [1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methanol (8.07 g, 39.1 mmol) and triethylamine (5.94 g, 58.7 mmol) in dichloromethane (50 mL) was cooled in a -30 °C dry ice/methanol bath under a nitrogen atmosphere. Methanesulfonyl chloride (4.93 g, 43.0 mmol) was added via syringe, and after 30 minutes the reaction mixture was poured into a separatory funnel containing 200 mL of dichloromethane and 100 mL of water. The organic layer was drawn off and washed sequentially with saturated sodium bicarbonate, 0.5 M HCl (50 mL), and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to 10.19 g of orange oil that crystallized upon standing. The solid was dissolved in DMF (35 mL) and treated with sodium azide (5.08 g, 78.2 mmol). After 3 hours, water (140 ml) was added, and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to 11.0 g of dark oil. Purification by prep HPLC (silica cartridge, eluting with 25% to 30% ethyl acetate in hexane) provided 6.95 g of 3-(azidomethyl)-1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole as a pale orange oil.

Part D

A mixture of 3-(azidomethyl)-1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole (5.32 g, 23.0 mmol), poly(methylhydrosiloxane) (6.0 g), butyltin tris(2-ethylhexanoate) (1.39 g, 2.3 mmol) and 1-propanol (6.91 g) was heated under a nitrogen atmosphere in an 80 °C oil bath for 4 hours. Dichloromethane (46 mL), triethylamine (4.65 g, 46.0 mmol), and 2,4-dichloro-3-nitroquinoline (8.39 g, 34.5 mmol) were added, and after stirring overnight at room temperature, the reaction was treated with water (50 mL) and methyl *tert*-butyl ether (50 mL). The product was collected by filtration, washed with water and excess methyl

tert-butyl ether, and dried on suction for 30 minutes to afford 7.28 g of 2-chloro-*N*-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-3-nitroquinolin-4-amine as a yellow solid.

Part E

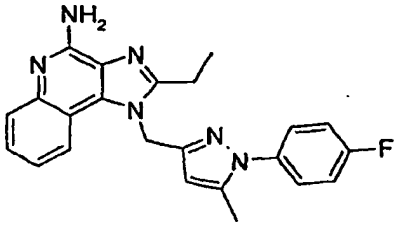
A mixture of 2-chloro-*N*-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-3-nitroquinolin-4-amine (10.0 g, 24.3 mmol), 5% platinum on carbon (1.0 g), and acetonitrile (150 mL) was placed under hydrogen pressure on a Parr apparatus. After 45 minutes, the mixture was filtered through a layer of CELITE and diluted with acetonitrile to a total volume of 300 mL. This stock solution of 2-chloro-N^4-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine was used in the subsequent steps.

Part F

To a portion of the stock solution of 2-chloro-N^4-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine in acetonitrile that was prepared in Part E (6.08 mmol) was added acetyl chloride (0.526 g, 6.7 mmol). The reaction was heated at reflux for 4 hours, and the resulting solid was collected by filtration, transferred to a 45 mL steel Parr vessel, treated with ammonia in methanol (25 mL of a 7 M solution), and heated in a 150 °C oven for 24 hours. The reaction mixture was concentrated, and the resulting solid was slurried in 2 M sodium carbonate and then collected by filtration. The filter cake was washed with water, dried on suction, and then purified by prep HPLC (silica cartridge, eluting with 20% to 45% CMA in chloroform). Recrystallization from acetonitrile afforded 0.972 g of 1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 239-240 °C. MS (ESI) m/z 387 $(M + H)^+$; Anal. Calcd for $C_{22}H_{19}FN_6$: C, 68.38; H, 4.96; N, 21.75. Found: C, 68.28; H, 4.85; N, 21.69.

Example 2

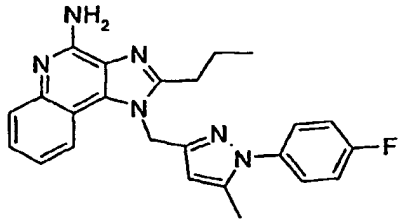
2-Ethyl-1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine



2-Chloro-N^4-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (6.08 mmol, prepared in Part E of Example 1) was treated with propionyl chloride (618 mg, 6.68 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Part F of Example 1. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 40% CMA in chloroform) followed by recrystallization from acetonitrile afforded 1.30 g of 2-ethyl-1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 246-247 °C. MS (ESI) m/z 401 $(M + H)^+$; Anal. Calcd for $C_{23}H_{21}FN_6$: C, 68.98; H, 5.29; N, 20.99. Found: C, 68.78; H, 5.27; N, 21.09.

Example 3

1-{[1-(4-Fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine

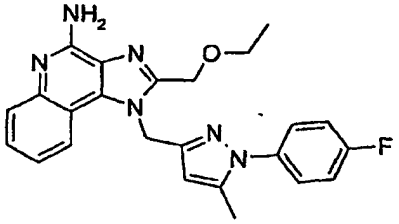


2-Chloro-N^4-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (3.04 mmol, prepared in Part E of Example 1) was treated with butyryl chloride (352 mg, 3.3 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Example Part F of Example 1. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 40% CMA in chloroform) followed by

recrystallization from acetonitrile afforded 670 mg of 1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 204-205 °C. MS (ESI) m/z 415 $(M + H)^+$; Anal. Calcd for $C_{24}H_{23}FN_6$: C, 69.55; H, 5.59; N, 20.28. Found: C, 69.47; H, 5.40; N, 20.54.

Example 4

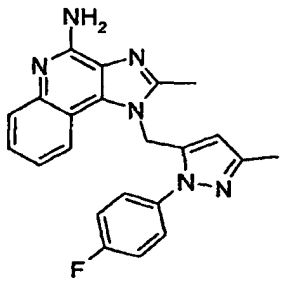
2-(Ethoxymethyl)-1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine



2-Chloro-N^4-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (3.04 mmol, prepared in Part E of Example 1) was treated with ethoxyacetyl chloride (404 mg, 3.3 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Example Part F of Example 1. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 45% CMA in chloroform) followed by recrystallization from acetonitrile afforded 830 mg of 2-(ethoxymethyl)-1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 175-176 °C. MS (ESI) m/z 431 $(M + H)^+$; Anal. Calcd for $C_{24}H_{23}FN_6O$: C, 66.96; H, 5.39; N, 19.52. Found: C, 66.77; H, 5.21; N, 19.30.

Example 5

1-{[1-(4-Fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

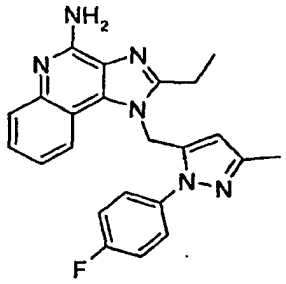
Ethyl 1-(4-fluorophenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (prepared in Part A of Example 1) was converted to 2-chloro-N^4-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}quinoline-3,4-diamine using the methods of Example 1, Parts B-E and obtained as a stock solution in acetonitrile. This stock solution was used in the subsequent steps.

Part B

To a portion of the stock solution of 2-chloro-N^4-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}quinoline-3,4-diamine in acetonitrile that was prepared in Part A (2.56 mmol) was added acetyl chloride (220 mg, 2.8 mmol). The reaction was heated at reflux for 2 hours, and the resulting solid was collected by filtration, transferred to a 45 mL steel Parr vessel, treated with ammonia in methanol (25 mL of a 7 M solution), and heated in a 150 °C oven for 24 hours. The reaction mixture was concentrated, and the resulting solid was slurried in 2 M sodium carbonate and then collected by filtration. The filter cake was washed with water, dried on suction, and then purified by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform). Recrystallization from acetonitrile, followed by drying (98 °C, 45 mtorr, 3.5 hours) afforded 390 mg of 1-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 246-248 °C. MS (ESI) m/z 387 $(M + H)^+$; Anal. Calcd for $C_{22}H_{19}FN_6$: C, 68.38; H, 4.96; N, 21.75. Found: C, 68.10; H, 4.91; N, 22.00.

Example 6

2-Ethyl-1-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine

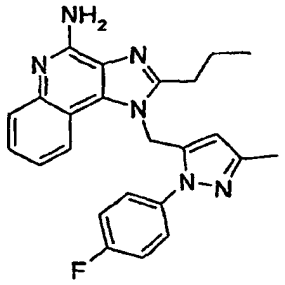


2-Chloro-N^4-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}quinoline-3,4-diamine (2.56 mmol, prepared in Part A of Example 5) was treated with propionyl chloride (259 mg, 2.8 mmol) and then with ammonia in methanol (25 mL of a 7 M

solution) according to Part B of Example 5. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from acetonitrile afforded 533 mg of 2-ethyl-1-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 280-282 °C. MS (ESI) m/z 401 $(M + H)^+$; Anal. Calcd for $C_{23}H_{21}FN_6$: C, 68.98; H, 5.29; N, 20.99. Found: C, 69.02; H, 5.16; N, 20.98.

Example 7

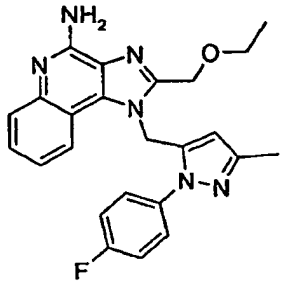
1-{[1-(4-Fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



2-Chloro-N^4-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}quinoline-3,4-diamine (2.56 mmol, prepared in Part A of Example 5) was treated with butyryl chloride (298 mg, 2.8 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Part B of Example 5. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from acetonitrile afforded 541 mg of 1-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 277-279 °C. MS (APCI) m/z 415 $(M + H)^+$; Anal. Calcd for $C_{24}H_{23}FN_6$: C, 69.55; H, 5.59; N, 20.28. Found: C, 69.51; H, 5.37; N, 20.47.

Example 8

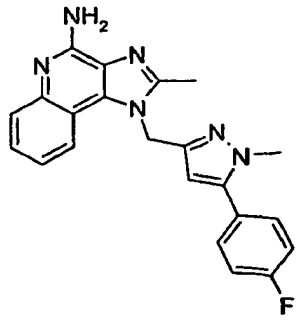
2-(Ethoxymethyl)-1-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine



2-Chloro-N^4-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}quinoline-3,4-diamine (5.12 mmol, prepared in Part A of Example 5) was treated with ethoxyacetyl chloride (690 mg, 5.63 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Part B of Example 5. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from acetonitrile afforded 1.144 g of 2-(ethoxymethyl)-1-{[1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 185-186 °C. MS (APCI) m/z 431 $(M + H)^+$; Anal. Calcd for $C_{24}H_{23}FN_6O$: C, 66.96; H, 5.39; N, 19.52. Found: C, 67.03; H, 5.34; N, 19.46.

Example 9

1-{[5-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A neat mixture of 4'-fluoroacetophenone (69.1 g, 0.500 mol) and diethyl oxalate (80.4 g, 0.550 mol) was added in one portion to a solution of sodium *tert*-butoxide (52.9 g,

0.550 mol) in ethanol (0.550 L). After one hour, ethanol (0.45 L) was added to assist the stirring, and the reaction was stirred for one additional hour. The solid was collected by filtration, washed with 1 L of ethanol, and dried on suction for 3.5 days to afford 116.5 g of ethyl 4-(4-fluorophenyl)-2,4-dioxobutanoate, sodium salt as a pale yellow solid.

Part B

A slurry of ethyl 4-(4-fluorophenyl)-2,4-dioxobutanoate, sodium salt (52.0 g, 0.200 mol) in ethanol (0.400 L) was treated with glacial acetic acid (12.6 mL, 0.220 mol) and methyl hydrazine (10.1 g, 0.220 mol). After 3.5 hours, the reaction mixture was concentrated, the salts were dissolved in water, and the aqueous layer was extracted with methyl *tert*-butyl ether (3x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to a pale yellow oil. The crude product was dissolved in 25% ethyl acetate in hexane (50 mL), divided into two equal portions, and each portion was purified by prep HPLC (silica cartridge, eluting with 30% to 50% ethyl acetate in hexane) to separate the two pyrazole isomers. The fractions from both purifications that contained the lower running isomer were combined and concentrated to yield 23.93 g of ethyl 5-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-3-carboxylate as an off-white solid. The fractions from both purifications that contained the higher running isomer were combined and concentrated to yield 20.02 g of ethyl 3-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-5-carboxylate as pale yellow needles.

Part C

Ethyl 5-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-3-carboxylate (23.93 g, 96.4 mmol) was converted to 2-chloro-N^4-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine using the methods of Example 1, Parts A-E and obtained as a stock solution in acetonitrile. This stock solution was used in the subsequent steps.

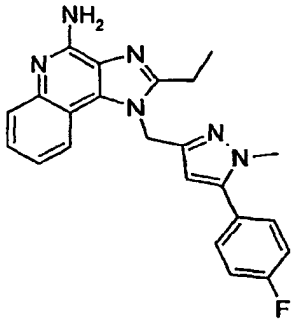
Part D

To a portion of the stock solution of 2-chloro-N^4-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine in acetonitrile that was prepared in Part C (3.8 mmol) was added acetyl chloride (330 mg, 4.2 mmol). The reaction was heated at reflux for 4 hours, and the resulting solid was collected by filtration, transferred to a 45 mL steel Parr vessel, treated with ammonia in methanol (25 mL of a 7 M solution), and heated in a 150 °C oven for 18 hours. The reaction mixture was concentrated, and the resulting solid was slurried in 2 M sodium carbonate and then collected by filtration. The

filter cake was washed with water, dried on suction, and then purified by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform). Recrystallization from acetonitrile afforded 634 mg of 1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 229-230 °C (phase transition at 218-220 °C). MS (ESI) m/z 387 $(M + H)^+$; Anal. Calcd for $C_{22}H_{19}FN_6$: C, 68.38; H, 4.96; N, 21.75. Found: C, 68.39; H, 4.83; N, 21.79.

Example 10

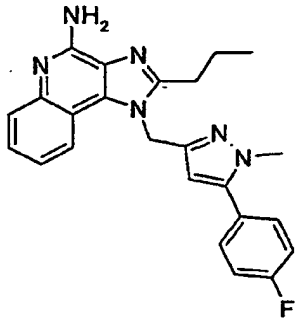
2-Ethyl-1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine



2-Chloro-N^4-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (3.8 mmol, prepared in Part C of Example 9) was treated with propionyl chloride (389 mg, 4.2 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Part D of Example 9. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from 30% methanol in acetonitrile afforded 344 mg of 2-ethyl-1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 260-261 °C. MS (ESI) m/z 401 $(M + H)^+$; Anal. Calcd for $C_{23}H_{21}FN_6$: C, 68.98; H, 5.29; N, 20.99. Found: C, 68.81; H, 5.20; N, 20.98.

Example 11

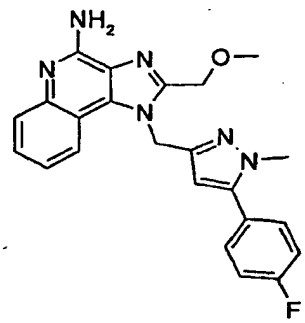
1-{[5-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



2-Chloro-N^4-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (3.8 mmol, prepared in Part C of Example 9) was treated with butyryl chloride (448 mg, 4.2 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Part D of Example 9. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from 20% methanol in acetonitrile afforded 621 mg of 1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 227-228 °C. MS (ESI) m/z 415 $(M + H)^+$; Anal. Calcd for $C_{24}H_{23}FN_6$: C, 69.55; H, 5.59; N, 20.28. Found: C, 69.48; H, 5.55; N, 20.31.

Example 12

1-{[5-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-(methoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

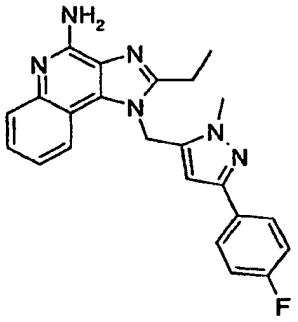


2-Chloro-N^4-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (7.6 mmol, prepared in Part C of Example 9) was treated with methoxyacetyl

chloride (912 mg, 8.4 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Part D of Example 9. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from acetonitrile afforded 1.003 g of 1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-(methoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 199-201 °C. MS (ESI) m/z 417 $(M + H)^+$; Anal. Calcd for $C_{23}H_{21}FN_6O$: C, 66.33; H, 5.08; N, 20.18. Found: C, 66.21; H, 4.96; N, 20.18.

Example 13

2-Ethyl-1-{[3-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of ethyl 3-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-5-carboxylate (8.86 g, 35.7 mmol, prepared in Part B of Example 9) in methanol (100 mL) and water (33 mL) was treated with lithium hydroxide monohydrate (5.99 g, 143 mmol), and the reaction was stirred for 5 hours. The methanol was evaporated under reduced pressure, and the residue was treated with hydrochloric acid (143 mL of a 1M solution). The resulting solid was collected by filtration, washed with water, and dried on suction to 7.37 g of 3-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-5-carboxylic acid as a white solid.

Part B

A suspension of 3-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-5-carboxylic acid (4.87 g, 22.1 mmol) in dichloromethane (100 mL) was treated with *N,N*-dimethylformamide (162 mg, 2.21 mmol) and oxalyl chloride (5.61 g, 44.2 mmol). After 2.5 hours, the reaction mixture was poured into ammonium hydroxide (100 mL of concentrated solution) while cooling on an ice bath. The dichloromethane was evaporated under reduced

pressure, and the solid was collected by filtration to afford 3-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-5-carboxamide as a white solid.

Part C

To a solution of 3-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-5-carboxamide (1.41 g, 6.43 mmol) in THF (10 mL) was added $LiAlH_4$ (7.7 mL of a 1M solution in THF), and the reaction was stirred at ambient temperature for 30 minutes, followed by stirring at reflux for 3 hours. The reaction was quenched by the addition of water (0.29 mL), 4N sodium hydroxide (0.29 mL), and water (0.88 mL). The resulting solid was removed by filtration through CELITE, and the filtrate was concentrated under reduced pressure. Purification by prep HPLC (silica cartridge, eluting with 25% to 50% CMA in chloroform) afforded 1.28 g of 1-[3-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methanamine as a white solid.

Part D

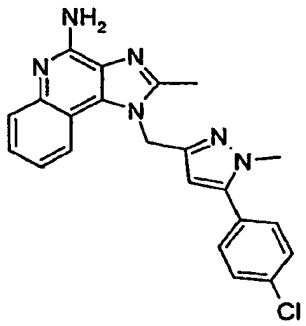
A solution of 1-[3-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methanamine (1.27 g, 6.19 mmol) and triethylamine (0.94 g, 9.3 mmol) in dichloromethane (50 mL) was treated with 2,4-dichloro-3-nitroquinoline (1.58 g, 6.50 mmol), and the reaction was stirred for 4 days. Additional 2,4-dichloro-3-nitroquinoline (318 mg, 1.31 mmol) was added, and after 2 additional days of stirring, water was added, the organic layer was drawn off, and the aqueous layer was extracted with chloroform (2x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Methyl *tert*-butyl ether was added, and the product was collected by filtration to afford 2.04 g of 2-chloro-*N*-{[3-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methyl}-3-nitroquinolin-4-amine as a yellow solid.

Part E

2-Chloro-*N*-{[3-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methyl}-3-nitroquinolin-4-amine (2.04 g, 4.95 mmol) was treated according to Parts E-F of Example 1. Purification of the crude product by prep HPLC (silica cartridge, eluting with 3% to 45% CMA in chloroform) followed by recrystallization from acetonitrile afforded 0.384 g of 2-ethyl-1-{[3-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 296-297 °C. MS (APCI) m/z 401 $(M + H)^+$; Anal. Calcd for $C_{23}H_{21}FN_6$: C, 68.98; H, 5.29; N, 20.99. Found: C, 68.93; H, 5.32; N, 20.97.

Example 14

1-{[5-(4-Chlorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

To a solution of 2-chloro-*N*-{[5-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-3-nitroquinolin-4-amine (2.40 g, 5.60 mmol, prepared according to step A of Example 1 and steps A-D of Example 13) in ethanol (25 mL) and acetonitrile (25 mL) was added sodium dithionite (4.88 g, 28.0 mmol in 10 mL of water). After 45 minutes, the solids were removed by filtration through CELITE. The filtrate was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was drawn off, and the aqueous layer was extracted with additional portions of ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 1.70 g of 2-chloro-N^4-{[5-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine as a yellow solid.

Part B

To a solution of 2-chloro-N^4-{[5-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (1.70 g, 4.27 mmol) in toluene (40 mL) was added triethyl orthoacetate (831 mg, 5.12 mmol) and pyridine hydrochloride (98 mg, 0.85 mmol). The solution was heated to reflux under a nitrogen atmosphere for 6 hours, an additional portion of pyridine hydrochloride (98 mg, 0.85 mmol) was added, and the reaction was heated at reflux overnight. The reaction mixture was diluted with dichloromethane, washed with a saturated solution of sodium bicarbonate, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to a brown solid. Purification by flash chromatography on silica gel (eluted with 3% to 4%

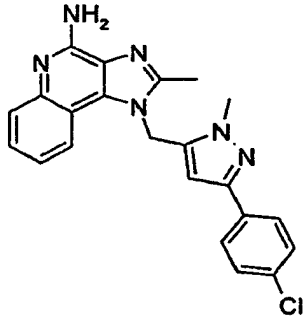
methanol in dichloromethane) afforded 1.21 g of 4-chloro-1-{[5-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinoline as a yellow solid.

Part C

4-Chloro-1-{[5-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinoline (1.21 g, 2.87 mmol) was heated with ammonia in methanol (30 mL of a 7M solution) in a steel Parr vessel for 16 hours. The reaction mixture was diluted with dichloromethane (100 mL), washed with a saturated solution of sodium bicarbonate, washed with brine, dried over magnesium sulfate, filtered, and concentrated to a pale yellow solid. Trituration with acetonitrile afforded 720 mg of 1-{[5-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 256-258 °C. MS (APCI) m/z 403 $(M + H)^+$; Anal. Calcd for $C_{22}H_{19}ClN_6$: C, 65.59; H, 4.75; N, 20.86. Found: C, 65.21; H, 4.81; N, 20.94.

Example 15

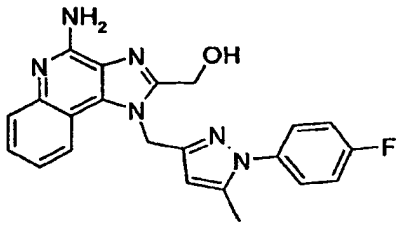
1-{[3-(4-Chlorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Prepared according to Parts A-C of Example 14. Purification of the crude product by flash chromatography on silica gel (eluting with 2% to 7% methanol in dichloromethane) followed by trituration with dichloromethane afforded 430 mg of 1-{[3-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methyl}-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder, mp >290 °C. MS (APCI) m/z 403 $(M + H)^+$; Anal. Calcd for $C_{22}H_{19}ClN_6 \cdot 0.2\ CH_2Cl_2$: C, 63.51; H, 4.66; N, 20.02. Found: C, 63.14; H, 4.53; N, 19.97.

Example 16

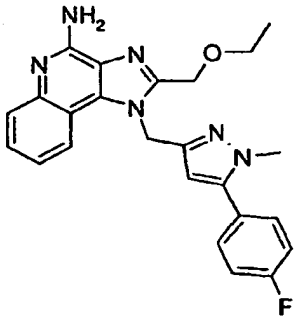
(4-Amino-1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methanol



The method described in Example 18 was used to convert 2-(ethoxymethyl)-1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (prepared as described in Example 4, 486 mg, 1.13 mmol) into 325 mg of (4-amino-1-{[1-(4-fluorophenyl)-5-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methanol, which was isolated as white needles following purification by prep HPLC (silica cartridge, eluting with 20% to 70% CMA in chloroform) and crystallization from acetonitrile/methanol, mp 264-266 °C. MS (ESI) m/z 403 $(M + H)^+$; Anal. Calcd for $C_{22}H_{19}FN_6O$: C, 65.66; H, 4.76; N, 20.88. Found: C, 65.42; H, 4.65; N, 21.10.

Example 17

2-(Ethoxymethyl)-1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine

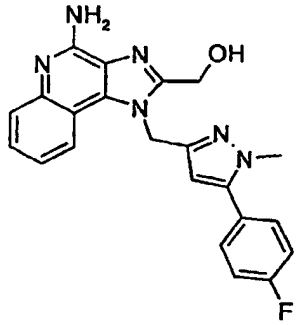


2-Chloro-N^4-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (3.8 mmol, prepared in Part C of Example 9) was treated with ethoxyacetyl chloride (4.2 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Part D of Example 9. Purification of the crude product by prep HPLC (silica

cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from acetonitrile afforded 461 mg of 2-(ethoxymethyl)-1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 194-195 °C. Anal. Calcd for $C_{24}H_{23}FN_6O$: C, 66.96; H, 5.39; N, 19.52. Found: C, 67.20; H, 5.18; N, 19.70.

Example 18

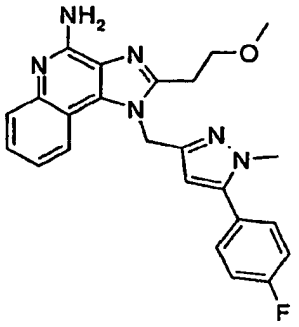
(4-Amino-1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methanol



A solution of 1 M boron tribromide in dichloromethane (8.1 mL, 8.1 mmol) was added to a solution of 1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-(methoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (prepared as described in Example 12, 676 mg, 1.62 mmol). A white precipitate formed and the mixture was stirred for 18 hours. Methanol (50 mL) was added and the mixture was concentrated under reduced pressure. A solution of 2 M sodium carbonate was added to the solid, which was isolated by filtration and washed with water. The crude solid was dried and purified by prep HPLC (silica cartridge, eluting with 20% to 70% CMA in chloroform). After recrystallization from acetontrile/methanol, 4-amino-1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methanol (402 mg) was isolated as white solid, mp 242-243 °C. MS (ESI) m/z 403 $(M + H)^+$; Anal. Calcd for $C_{22}H_{19}FN_6O \cdot 0.2\ H_2O$: C, 65.07; H, 4.82; N, 20.70. Found: C, 64.80; H, 4.47; N, 20.88.

Example 19

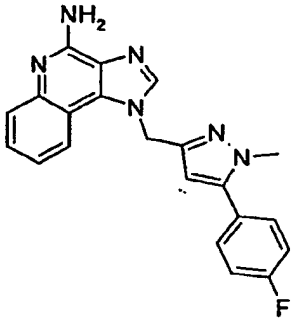
1-{[5-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



2-Chloro-N^4-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (3.5 g, 9.2 mmol, prepared in Part C of Example 9) was treated with 3-methoxypropionyl chloride (1.14 g, 10.1 mmol) and then with ammonia in methanol (25 mL of a 7 M solution) according to Part D of Example 9. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from acetonitrile afforded 1.15 g of 1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 257-261 °C. MS (ESI) m/z 431 $(M + H)^+$; Anal. Calcd for $C_{24}H_{23}FN_6O$: C, 66.96; H, 5.39; N, 19.52. Found: C, 66.97; H, 5.19; N, 19.43.

Example 20

1-{[5-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine

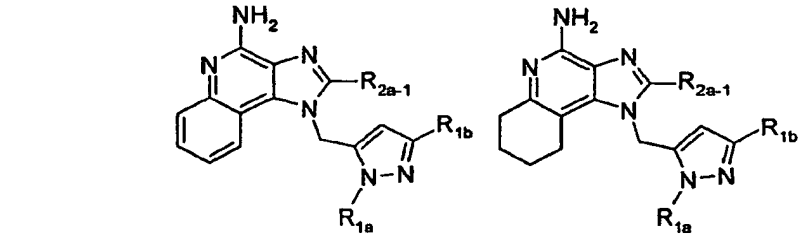


2-Chloro-N^4-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}quinoline-3,4-diamine (4.6 mmol, prepared in Part C of Example 9) was treated with triethylorthoformate (1.02 g, 6.9 mmol) and pyridine hydrochloride (53 mg, 0.46 mmol) in toluene (25 mL). The mixture was heated at reflux for 4 hours, then was stirred at room

temperature overnight. A solid was isolated by filtration and was treated with ammonia in methanol (25 mL of a 7 M solution) according to Part D of Example 9. Purification of the crude product by prep HPLC (silica cartridge, eluting with 10% to 50% CMA in chloroform) followed by recrystallization from acetonitrile afforded 635 g of 1-{[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 224-225 °C. MS (ESI) m/z 373 $(M + H)^+$; Anal. Calcd for $C_{21}H_{17}FN_6$: C, 67.73; H, 4.60; N, 22.57. Found: C, 67.71; H, 4.45; N, 22.70.

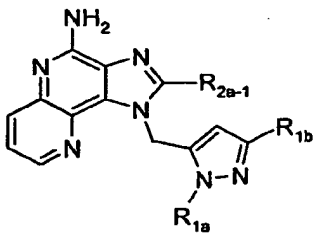
Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IIa, IIIa, IVa, VIIa, or Xa), an R_{1a} substituent, an R_{1b} substituent, and an R_{2a-1} substituent shown in the following table, wherein each line of the table is matched with the Formula (IIa, IIIa, IVa, VIIa, or Xa) to represent a specific embodiment.

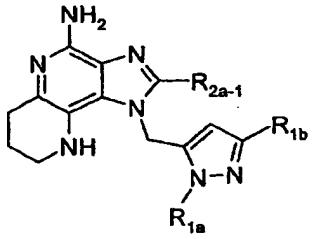


IIa

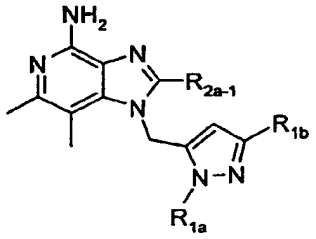
IIIa



IVa



VIIa



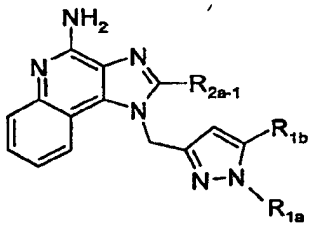
Xa

R_{1a}	R_{1b}	R_{2a-1}
methyl	4-chlorophenyl	methyl
methyl	4-fluorophenyl	methyl
4-fluorophenyl	methyl	methyl

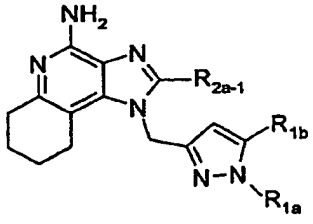
4-chlorophenyl	methyl	methyl
methyl	4-chlorophenyl	ethyl
methyl	4-fluorophenyl	ethyl
4-fluorophenyl	methyl	ethyl
4-chlorophenyl	methyl	ethyl
methyl	4-chlorophenyl	*n*-propyl
methyl	4-fluorophenyl	*n*-propyl
4-fluorophenyl	methyl	*n*-propyl
4-chlorophenyl	methyl	*n*-propyl
methyl	4-chlorophenyl	*n*-butyl
methyl	4-fluorophenyl	*n*-butyl
4-fluorophenyl	methyl	*n*-butyl
4-chlorophenyl	methyl	*n*-butyl
methyl	4-chlorophenyl	methoxymethyl
methyl	4-fluorophenyl	methoxymethyl
4-fluorophenyl	methyl	methoxymethyl
4-chlorophenyl	methyl	methoxymethyl
methyl	4-chlorophenyl	ethoxymethyl
methyl	4-fluorophenyl	ethoxymethyl
4-fluorophenyl	methyl	ethoxymethyl
4-chlorophenyl	methyl	ethoxymethyl
methyl	4-chlorophenyl	2-methoxyethyl
methyl	4-fluorophenyl	2-methoxyethyl
4-fluorophenyl	methyl	2-methoxyethyl
4-chlorophenyl	methyl	2-methoxyethyl
methyl	4-chlorophenyl	hydroxymethyl
methyl	4-fluorophenyl	hydroxymethyl
4-fluorophenyl	methyl	hydroxymethyl
4-chlorophenyl	methyl	hydroxymethyl
methyl	4-chlorophenyl	2-hydroxyethyl
methyl	4-fluorophenyl	2-hydroxyethyl

4-fluorophenyl	methyl	2-hydroxyethyl
4-chlorophenyl	methyl	2-hydroxyethyl

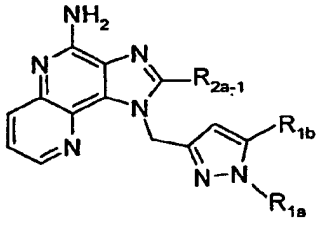
Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IIb, IIIb, IVb, VIIb, or Xb), an R_{1a} substituent, an R_{1b} substituent, and an R_{2a-1} substituent shown in the following table, wherein each line of the table is matched with the Formula (IIb, IIIb, IVb, VIIb, or Xb) to represent a specific embodiment.



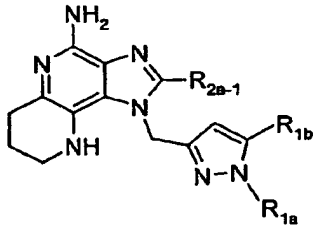
IIb



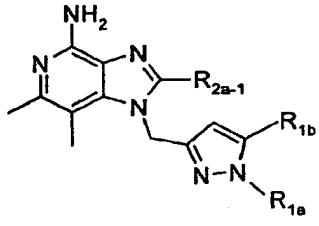
IIIb



IVb



VIIb



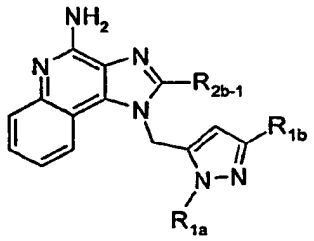
Xb

R_{1a}	R_{1b}	R_{2a-1}
methyl	4-chlorophenyl	methyl
methyl	4-fluorophenyl	methyl
4-fluorophenyl	methyl	methyl
4-chlorophenyl	methyl	methyl
methyl	4-chlorophenyl	ethyl
methyl	4-fluorophenyl	ethyl
4-fluorophenyl	methyl	ethyl
4-chlorophenyl	methyl	ethyl
methyl	4-chlorophenyl	*n*-propyl

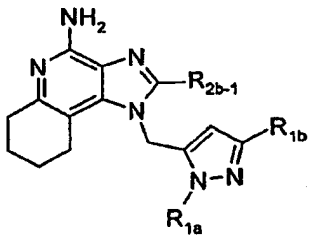
methyl	4-fluorophenyl	*n*-propyl
4-fluorophenyl	methyl	*n*-propyl
4-chlorophenyl	methyl	*n*-propyl
methyl	4-chlorophenyl	*n*-butyl
methyl	4-fluorophenyl	*n*-butyl
4-fluorophenyl	methyl	*n*-butyl
4-chlorophenyl	methyl	*n*-butyl
methyl	4-chlorophenyl	methoxymethyl
methyl	4-fluorophenyl	methoxymethyl
4-fluorophenyl	methyl	methoxymethyl
4-chlorophenyl	methyl	methoxymethyl
methyl	4-chlorophenyl	ethoxymethyl
methyl	4-fluorophenyl	ethoxymethyl
4-fluorophenyl	methyl	ethoxymethyl
4-chlorophenyl	methyl	ethoxymethyl
methyl	4-chlorophenyl	2-methoxyethyl
methyl	4-fluorophenyl	2-methoxyethyl
4-fluorophenyl	methyl	2-methoxyethyl
4-chlorophenyl	methyl	2-methoxyethyl
methyl	4-chlorophenyl	hydroxymethyl
methyl	4-fluorophenyl	hydroxymethyl
4-fluorophenyl	methyl	hydroxymethyl
4-chlorophenyl	methyl	hydroxymethyl
methyl	4-chlorophenyl	2-hydroxyethyl
methyl	4-fluorophenyl	2-hydroxyethyl
4-fluorophenyl	methyl	2-hydroxyethyl
4-chlorophenyl	methyl	2-hydroxyethyl

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IIc, IIIc, IVc, VIIc, or Xc), an R_{1a} substituent, an R_{1b} substituent, and an $R_{2b\text{-}1}$ substituent shown in the following table, wherein each line of

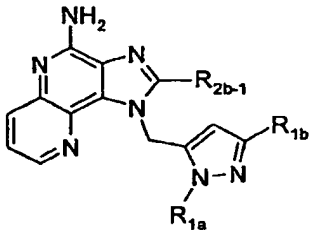
the table is matched with the Formula (IIc, IIIc, IVc, VIIc, or Xc) to represent a specific embodiment.



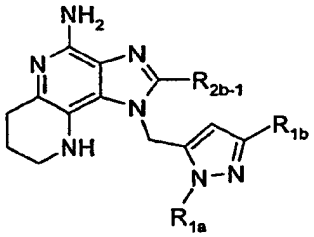
IIc



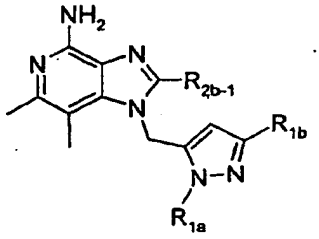
IIIc



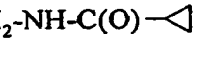
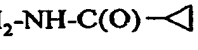
IVc



VIIc

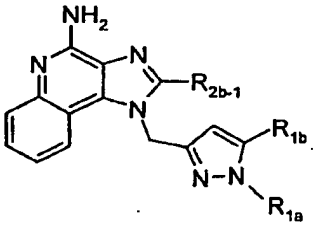


Xc

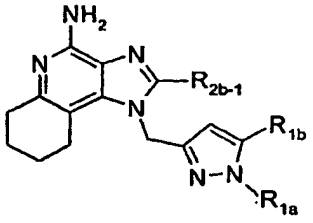
R_{1a}	R_{1b}	R_{2b-1}
methyl	4-chlorophenyl	$-CH_2-NH-S(O)_2-CH_3$
methyl	4-fluorophenyl	$-CH_2-NH-S(O)_2-CH_3$
4-fluorophenyl	methyl	$-CH_2-NH-S(O)_2-CH_3$
4-chlorophenyl	methyl	$-CH_2-NH-S(O)_2-CH_3$
methyl	4-chlorophenyl	$-CH_2-NH-S(O)_2-CH_2CH_3$
methyl	4-fluorophenyl	$-CH_2-NH-S(O)_2-CH_2CH_3$
4-fluorophenyl	methyl	$-CH_2-NH-S(O)_2-CH_2CH_3$
4-chlorophenyl	methyl	$-CH_2-NH-S(O)_2-CH_2CH_3$
methyl	4-chlorophenyl	$-CH_2-NH-C(O)-CH_3$
methyl	4-fluorophenyl	$-CH_2-NH-C(O)-CH_3$
4-fluorophenyl	methyl	$-CH_2-NH-C(O)-CH_3$
4-chlorophenyl	methyl	$-CH_2-NH-C(O)-CH_3$
methyl	4-chlorophenyl	
methyl	4-fluorophenyl	

4-fluorophenyl	methyl	—CH_2-NH-C(O)—◁
4-chlorophenyl	methyl	—CH_2-NH-C(O)—◁
methyl	4-chlorophenyl	-CH_2-NH-C(O)-N(H)CH_3
methyl	4-fluorophenyl	-CH_2-NH-C(O)-N(H)CH_3
4-fluorophenyl	methyl	-CH_2-NH-C(O)-N(H)CH_3
4-chlorophenyl	methyl	-CH_2-NH-C(O)-N(H)CH_3
methyl	4-chlorophenyl	-CH_2-NH-C(O)-N(CH_3)CH_3
methyl	4-fluorophenyl	-CH_2-NH-C(O)-N(CH_3)CH_3
4-fluorophenyl	methyl	-CH_2-NH-C(O)-N(CH_3)CH_3
4-chlorophenyl	methyl	-CH_2-NH-C(O)-N(CH_3)CH_3

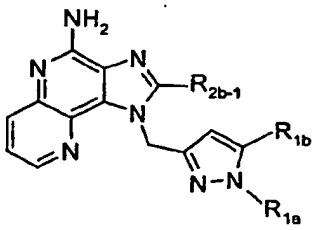
Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IId, IIId, IVd, VIId, or Xd), an R_{1a} substituent, an R_{1b} substituent, and an R_{2b-1} substituent shown in the following table, wherein each line of the table is matched with the Formula (IId, IIId, IVd, VIId, or Xd) to represent a specific embodiment.



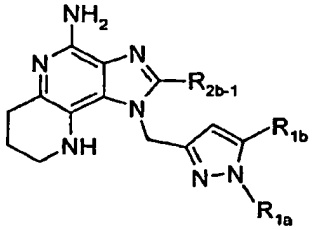
IId



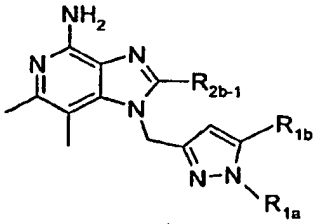
IIId



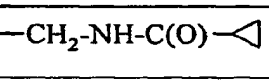
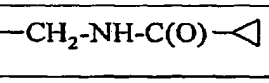
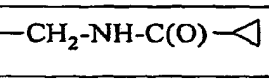
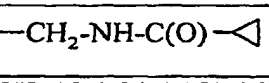
IVd



VIId



Xd

R_{1a}	R_{1b}	R_{2b-1}
methyl	4-chlorophenyl	$-CH_2-NH-S(O)_2-CH_3$
methyl	4-fluorophenyl	$-CH_2-NH-S(O)_2-CH_3$
4-fluorophenyl	methyl	$-CH_2-NH-S(O)_2-CH_3$
4-chlorophenyl	methyl	$-CH_2-NH-S(O)_2-CH_3$
methyl	4-chlorophenyl	$-CH_2-NH-S(O)_2-CH_2CH_3$
methyl	4-fluorophenyl	$-CH_2-NH-S(O)_2-CH_2CH_3$
4-fluorophenyl	methyl	$-CH_2-NH-S(O)_2-CH_2CH_3$
4-chlorophenyl	methyl	$-CH_2-NH-S(O)_2-CH_2CH_3$
methyl	4-chlorophenyl	$-CH_2-NH-C(O)-CH_3$
methyl	4-fluorophenyl	$-CH_2-NH-C(O)-CH_3$
4-fluorophenyl	methyl	$-CH_2-NH-C(O)-CH_3$
4-chlorophenyl	methyl	$-CH_2-NH-C(O)-CH_3$
methyl	4-chlorophenyl	
methyl	4-fluorophenyl	
4-fluorophenyl	methyl	
4-chlorophenyl	methyl	
methyl	4-chlorophenyl	$-CH_2-NH-C(O)-N(H)CH_3$
methyl	4-fluorophenyl	$-CH_2-NH-C(O)-N(H)CH_3$
4-fluorophenyl	methyl	$-CH_2-NH-C(O)-N(H)CH_3$
4-chlorophenyl	methyl	$-CH_2-NH-C(O)-N(H)CH_3$
methyl	4-chlorophenyl	$-CH_2-NH-C(O)-N(CH_3)CH_3$
methyl	4-fluorophenyl	$-CH_2-NH-C(O)-N(CH_3)CH_3$
4-fluorophenyl	methyl	$-CH_2-NH-C(O)-N(CH_3)CH_3$
4-chlorophenyl	methyl	$-CH_2-NH-C(O)-N(CH_3)CH_3$

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α, or interferon α and tumor necrosis factor α in human cells when tested using one of the methods described below.

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology, 58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x

10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the

reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS

(High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples

with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) on each plate. The solution of test compound is added at 7.5 mM to the first well of a dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μM) than the final tested concentration range.

Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014 μM) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is $2x10^6$ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4°C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70°C until analysis.

Interferon-α and Tumor Necrosis Factor-α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF-α and human IFN-α that have been pre-coated on specific spots. Each well contains four spots: one human TNF-α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine serum albumin spots. The human TNF-α capture and detection antibody pair is from MesoScale Discovery. The human IFN-α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN-α subtypes except IFN-α F (IFNA21). Standards consist of recombinant human TNF-α (R&D Systems, Minneapolis, MN) and IFN-α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of

analysis to each MSD plate. Two human IFN-α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the IFN-α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α or IFN-α (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN-α, TNF-α) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment

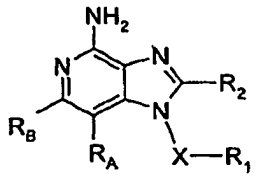
ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

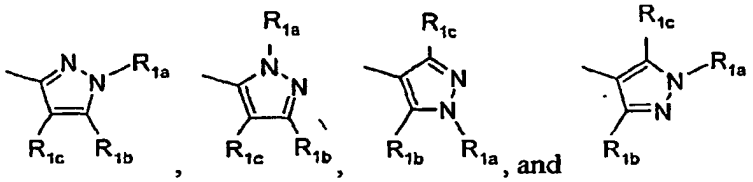
1. A compound of the Formula I:



I

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form either a fused heteroaryl ring that is unsubstituted or substituted by one or more R_b groups, or a 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, and that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,
alkoxy,
alkylthio, and
$-N(R_5)_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:
hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,

heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;

(dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

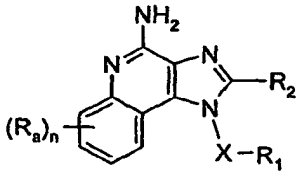
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_5)$-; and

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

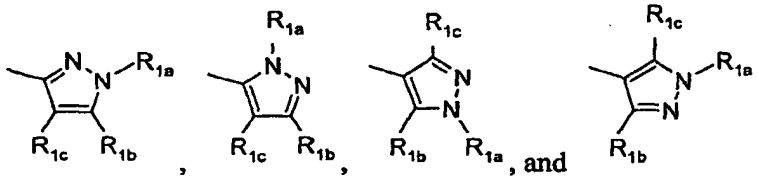
2. A compound of the Formula II:



II

wherein:

R_1 is selected from the group consisting of:



; and

X is selected from the group consisting of -$CH(R_3)$- and -$CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, $-N(R_5)_2$, and $-N(R_5)-Q-R_7$; and with the further proviso that only one of R_{1b} and R_{1c} can be $-N(R_5)_2$ or $-N(R_5)-Q-R_7$;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

n is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

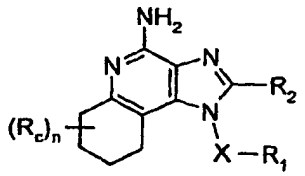
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

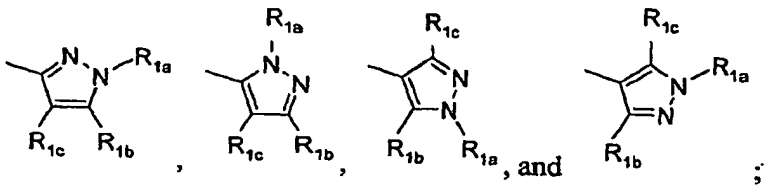
3. A compound of the Formula III:



III

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -$CH(R_3)$- and -$CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

n is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

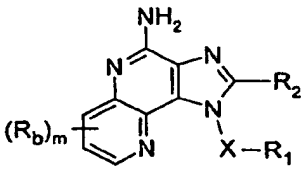
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_5)$-; and

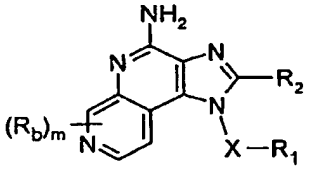
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

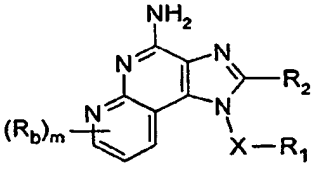
4. A compound selected from the group consisting of the Formulas IV, V, and VI:



IV



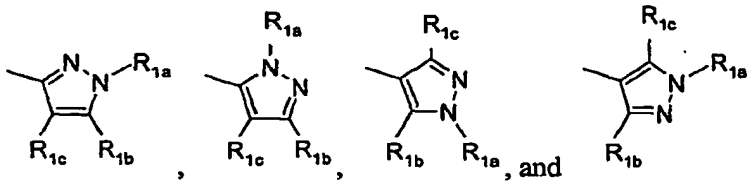
V



VI

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-$S(O)_{0-2}$-alkyl,

-$S(O)_{0-2}$-aryl,

-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

m is 0, 1, 2, or 3;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups

can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

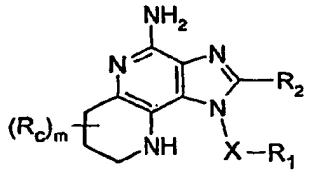
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

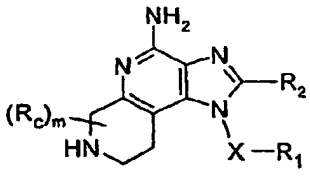
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

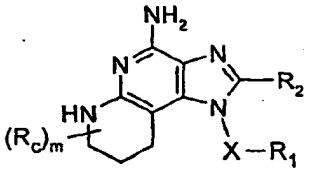
5. A compound selected from the group consisting of the Formulas VII, VIII, and IX:



VII



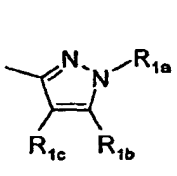
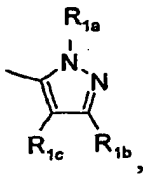
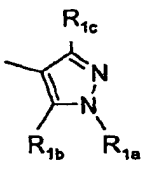
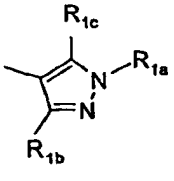
VIII



IX

wherein:

R_1 is selected from the group consisting of:


, 
, 
, and 
;

X is selected from the group consisting of $-CH(R_3)-$ and $-CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$,

$-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

m is 0, 1, 2, or 3;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

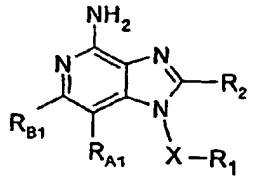
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_5)-; and

W is selected from the group consisting of a bond, -C(O)-, and -S(O)$_2$-;

or a pharmaceutically acceptable salt thereof.

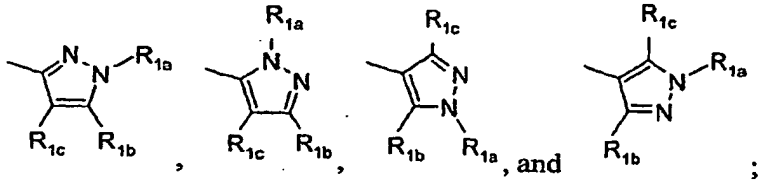
6. A compound of the Formula X:



X

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_5)$_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

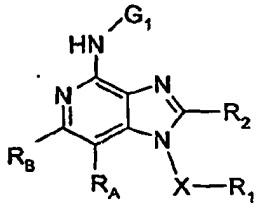
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_5)-; and

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;

or a pharmaceutically acceptable salt thereof.

7. A compound of the Formula XI:



XI

wherein:

G_1 is selected from the group consisting of:

-C(O)-R",

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R",

-C(O)-N(R'")R",

$-C(=NY_1)-R"$,

$-CH(OH)-C(O)-OY_1$,

$-CH(OC_{1-4}\text{ alkyl})Y_0$,

$-CH_2Y_2$, and

$-CH(CH_3)Y_2$;

R" and R'" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R'" can also be hydrogen;

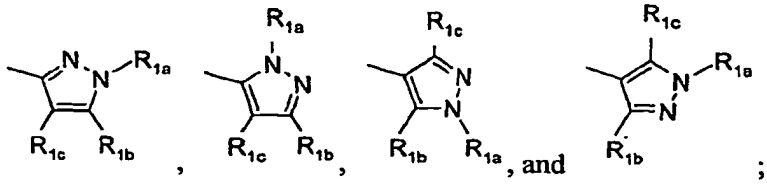
α-aminoacyl is an α-aminoacyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y_1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl; and

Y_2 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -$CH(R_3)$- and -$CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form either a fused heteroaryl ring that is unsubstituted or substituted by one or more R_b groups, or a 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, and that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-$N(R_5)_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_4)_2$,

-N(R_4)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-,

$-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

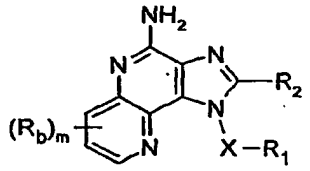
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

8. The compound or salt of claim 6 wherein R_{A1} and R_{B1} are each methyl.

9. The compound or salt of claim 2 or claim 3 wherein n is 0.

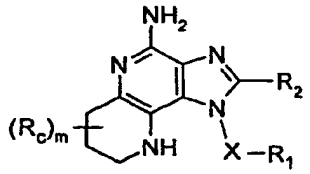
10. The compound or salt of claim 4 wherein the compound is Formula IV:



IV

or a pharmaceutically acceptable salt thereof.

11. The compound or salt of claim 5 wherein the compound is Formula VII:



VII

or a pharmaceutically acceptable salt thereof.

12. The compound or salt of any one of claims 4, 5, 10, and 11 wherein m is 0.

13. The compound or salt of any one of claims 1 through 12 wherein R_2 is R_{2a}.

14. The compound or salt of claim 13 wherein R_{2a} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4}alkyl-O-C_{1-4}alkylenyl, and hydroxyC_{1-4}alkylenyl.

15. The compound or salt of claim 14 wherein R_{2a} is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

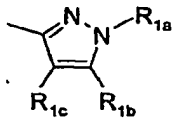
16. The compound or salt of any one of claims 1 through 12 wherein R_2 is R_{2b}.

17. The compound or salt of claim 16 wherein R_{2b} is $-CH_2-NH-SO_2-CH_3$ or $-CH_2-NH-SO_2-CH_2CH_3$.

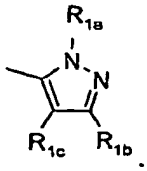
18. The compound or salt of any one of claims 1 through 17 wherein X is C_{1-4} alkylene.

19. The compound or salt of claim 18 wherein X is $-CH_2-$.

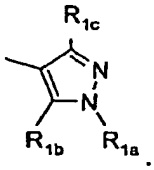
20. The compound or salt of any one of claims 1 through 19 wherein R_1 is



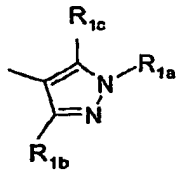
21. The compound or salt of any one of claims 1 through 19 wherein R_1 is



22. The compound or salt of any one of claims 1 through 19 wherein R_1 is



23. The compound or salt of any one of claims 1 through 19 wherein R_1 is



24. The compound or salt of any one of claims 1 through 23 wherein R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl, wherein alkyl, aryl, and heteroaryl are each unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and haloalkyl.

25. The compound or salt of claim 24 wherein not more than one of R_{1a}, R_{1b}, and R_{1c} is aryl or heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and haloalkyl.

26. The compound or salt of claim 24 or 25 wherein at least one of R_{1a}, R_{1b}, and R_{1c} is other than hydrogen.

27. The compound or salt of claim 24 or 25 wherein one of R_{1a}, R_{1b}, and R_{1c} is hydrogen.

28. The compound or salt of claim 27 wherein R_{1c} is hydrogen.

29. The compound or salt of any one of claims 24 through 28 wherein R_{1a} and R_{1b} are independently selected from the group consisting of C_{1-4} alkyl and aryl which is unsubstituted or substituted by one or more substituents independently selected from fluoro and chloro, and R_{1c} is hydrogen.

30. The compound or salt of claim 29 wherein R_{1a} and R_{1b} are each independently selected from the group consisting of methyl, 4-fluorophenyl, and 4-chlorophenyl.

31. The compound or salt of any one of claims 24 through 29 wherein R_{1a} is C_{1-4} alkyl, R_{1b} is aryl which is unsubstituted or substituted by one or more substituents independently selected from fluoro and chloro, and R_{1c} is hydrogen.

32. The compound or salt of any one of claims 24 through 29 wherein R_{1a} is aryl which is unsubstituted or substituted by one or more substituents independently selected from fluoro and chloro, R_{1b} is C_{1-4} alkyl, and R_{1c} is hydrogen.

33. The compound or salt of claim 31 or 32 wherein aryl is 4-fluorophenyl or 4-chlorophenyl, and C_{1-4} alkyl is methyl.

34. The compound or salt of any one of claims 1 through 23 wherein R_{1b} or R_{1c} is $-N(R_5)-Q-R_7$; wherein R_5 is hydrogen or C_{1-4} alkyl, Q is -C(O)-, $-S(O)_2-$, or -C(O)-N(R_8), R_8 is hydrogen or C_{1-4} alkyl, and R_7 is alkyl, aryl, heteroaryl, or heterocyclyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl and heterocyclyl, oxo.

35. The compound or salt of claim 34 wherein R_{1c} is $-N(R_5)-Q-R_7$, and R_{1a} and R_{1b} are each independently selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl, wherein alkyl, aryl, and heteroaryl are each unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and haloalkyl.

36. The compound or salt of claim 34 wherein R_{1b} is $-N(R_5)-Q-R_7$, and R_{1a} and R_{1c} are each independently selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl, wherein alkyl, aryl, and heteroaryl are each unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and haloalkyl.

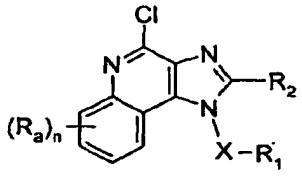
37. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 36 and a pharmaceutically acceptable carrier.

38. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one claims 1 through 36 or the pharmaceutical composition of claim 37 to the animal.

39. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 36 or the pharmaceutical composition of claim 37 to the animal.

40. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 36 or the pharmaceutical composition of claim 37 to the animal.

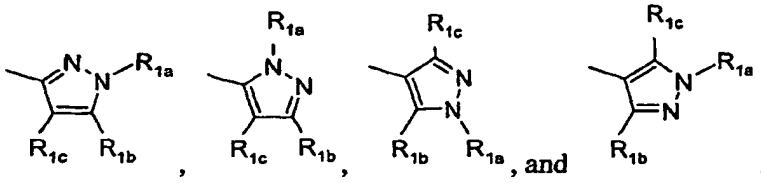
41. A compound of the Formula XII:



XII

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of $-CH_2-NH-SO_2-CH_3$, $-CH_2-NH-SO_2-CH_2CH_3$, $-CH_2-NH-C(O)-C_{1-4}$alkyl, and $-CH_2-NH-C(O)-N(R')R'$ wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_8 is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

n is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and

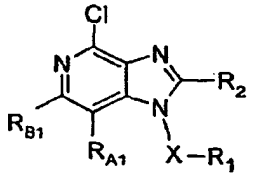
heteroaryl-C_{1-10}alkylenyl;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_5)$-; and

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

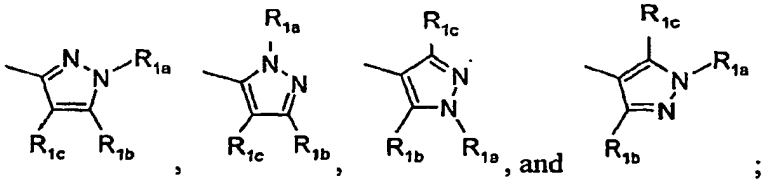
42. A compound of the Formula XIII:



XIII

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -$CH(R_3)$- and -$CH(R_3)$-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_5)_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

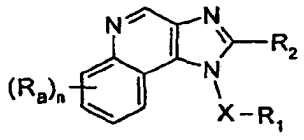
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_5)-; and

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;

or a pharmaceutically acceptable salt thereof.

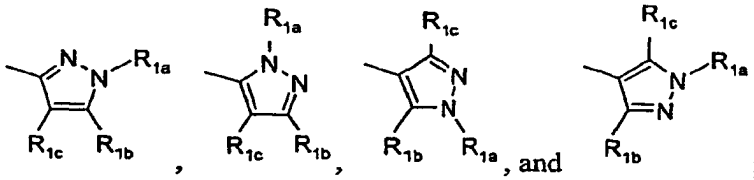
43. A compound of the Formula XIV:



XIV

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

n is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

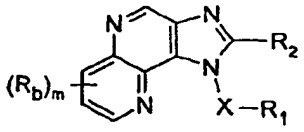
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_5)$-; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

or a pharmaceutically acceptable salt thereof.

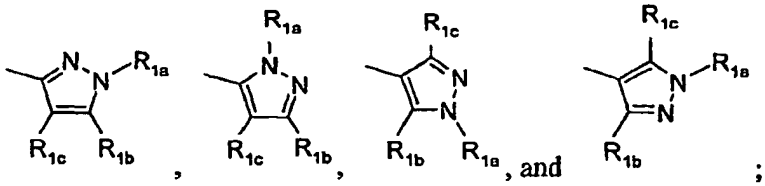
44. A compound of the Formula XV:



XV

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of -CH(R_3)- and -CH(R_3)-alkylene-;

R_2 is selected from the group consisting of R_{2a} and R_{2b} wherein:

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl; and

R_{2b} is selected from the group consisting of -CH_2-NH-SO_2-CH_3, -CH_2-NH-SO_2-CH_2CH_3, -CH_2-NH-C(O)-C_{1-4}alkyl, and -CH_2-NH-C(O)-N(R')R' wherein each R' is independently hydrogen, methyl or ethyl;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-$S(O)_{0-2}$-alkyl,

-$S(O)_{0-2}$-aryl,

-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

m is 0, 1, 2, or 3;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups

can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

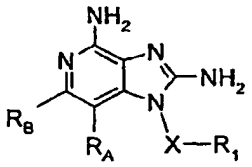
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

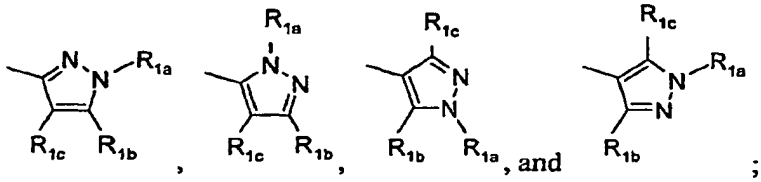
45. A compound of the Formula Ia:



Ia

wherein:

R_1 is selected from the group consisting of:



;

X is selected from the group consisting of $-CH(R_3)-$ and $-CH(R_3)$-alkylene-;

R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form either a fused heteroaryl ring that is unsubstituted or substituted by one or more R_b groups, or a 5 to 7 membered saturated ring

containing one heteroatom selected from the group consisting of N and S, and that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_5)_2$;

R_{1a}, R_{1b}, and R_{1c} are each independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_4)$_2$,
-N(R_4)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

with the proviso that each of R_{1b} and R_{1c} can be further independently selected from the group consisting of halogen, -N(R_5)$_2$, and -N(R_5)-Q-R_7; and with the further proviso that only one of R_{1b} and R_{1c} can be -N(R_5)$_2$ or -N(R_5)-Q-R_7;

R_a is selected from the group consisting of alkyl, alkoxy, fluoro, chloro, and trifluoromethyl;

R_b is selected from the group consisting of alkyl, alkoxy, hydroxy, fluoro, chloro, and trifluoromethyl;

R_c is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

R_3 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl;

R_5 is selected from the group consisting of hydrogen and alkyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_5)-$; and

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/049307

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04(2006.01)i, C07D 471/14(2006.01)i, C07D 231/00(2006.01)i, C07D 231/02(2006.01)i, C07D 471/22(2006.01)i, A61K 31/4745(2006.01)i, A61K 31/4738(2006.01)i, A61P 31/12(2006.01)i, A61P 31/00(2006.01)i, A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN(REGISTRY, CA), KIPO-INTRANET, DELPHION

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6664260 B2 (3M Innovative Properties Company) 16 December 2003 see the whole document.	1-37, 41-45
A	US 6514985 B1 (3M Innovative Properties Company) 04 February 2003 see the whole document.	1-37, 41-45

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 JUNE 2007 (14.06.2007)	**14 JUNE 2007 (14.06.2007)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea	LEE, MIN JUNG
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5603

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/049307

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 38-40
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 38-40 pertain to methods for treatment of the human or animal body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) or the PCT and Rule 39.1(iv) of the Regulations under PCT, to search

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2006/049307

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6664260 B2	16.12.2003	US 2003065005 A1	03.04.2003
		US 2004072858 A1	15.04.2004
US 6514985 B1	04.02.2003	US 2002173653 A1	21.11.2002
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